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APPLICATION OF MATHEMATICAL MODELING TO ANALYSIS OF IMMUNOLOGICAL PHENOMENA

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 4-14

[Article by V. N. Krut'ko, submitted 16 Jun 80]

[English abstract from source] The paper reviews mathematical models of immunological processes associated with reactions of the total immunity system and its single formations: infectious diseases, in vivo experiments with cell cultures, cell proliferation and differentiation in the thymus, primary and secondary immune responses to the antigen, immunodeficient states, etc. It also gives models of immunological reactions in vitro: precipitation, agglutination, plaque formation, etc. The paper contains a short description of potentialities of mathematical models of biological processes.

[Text] 1. Introduction

Space flight factors alter the immunological status of animals and man [1-6]. In particular, one observes involution of lymphoid tissue [3, 4, 6], elevation of autoantibody titer [2, 5], diminished immunoreactivity [1, 2], which increases the probability of disease in the presence of altered microbial profile in a spacecraft. The set of changes that occur in the immunity system during space flights is considered to be one of the main syndromes that must be given attention in the medical monitoring system [1].

The method of mathematical modeling of immunological phenomena, which is being used more and more at the present time, is one of the effective tools for studying the mechanisms of the immunity system. Quite often, the use of this method yields additional information about a phenomenon under study. In some cases, for example, analysis of "clasterization" [clustering or fragmentation?] processes in receptors that are cross-linked with antigen and are situated on the surface of lymphocytes [7-14], exact description and, consequently, comprehension of the phenomenon under study would be utterly impossible without the use of mathematics.

The purpose of this survey was to shed light on the current status of application of mathematical models to immunology. Moreover, it was deemed interesting to illustrate the capabilities of this method, which is not yet familiar enough to a broad circle of immunologists and which is apparently quite promising for solving problems of space immunology.

2. Modeling of Immunity System as a Whole

It is convenient to group the studies mentioned in his survey according to their relevance to a particular set of immunological phenomena. The first group refers to studies, in which models are described that simulate processes occurring in the integral immunity system of a living organism and the second, to studies dealing with modeling of individual immunological phenomena.

2.1. Models based on clone breeding theory

Clone breeding theory of Burnet [15], which was largely instrumental in stimulating development of immunology in the last two decades, served as the basis for a number of theoretical studies [16-34]. This theory is described the most comprehensively in the works of Bell [21-24]. In addition to postulates of this theory, in building his models the author used the hypothesis concerning the mechanisms of control of development of immunocyte clones by the number of antigen-bound receptors on the cell surface. It was assumed that if the share of receptors with antigen is too large either the cells perish or the rate of their proliferation is inhibited; with increase in share of bound receptors there is an increase in probability of differentiation of B cells into plasmocytes and decreased probability of their differentiation into memory cells. The models of Bell are systems of linear differential equations for the rates of change in concentrations of precursor cells referable to different clones, B cells, plasmocytes, antibodies, as well as antigen in the organism. The amount of bound and free receptors, antibodies and antigen is determined with a system of algebraic equations describing the chemical equilibrium in reactions between these components. The author discusses variants of models for the case of immunization with monovalent and polyvalent antigens. The results of modeling revealed that consideration of polyvalence does not lead to appreciable differences in dynamics of the components considered of the immune reaction in situations of real tests of practical interest, when the antigen concentration is substantially greater than the concentration of cell receptors. One should take into consideration the effects of polyvalence when using microdoses of antigen for immunization, as well as antigens with many antigenic determinants. In the case of 10 or fewer determinants, the antigen can be viewed as a set of independently functioning antigenic determinants.

A study of this model enabled Bell to formulate several interesting conclusions. Thus, he made an evaluation of the critical share of bound receptors (10%) needed to stimulate B cells for proliferation and differentiation. It was demonstrated that a change in number of receptors on the cell, in the range of 10^3-10^7, does not alter the response appreciably if the concentration of antigen is significantly higher than that of the cell receptors. It was illustrated that, by selecting a suitable immunization procedure, one can obtain complete tolerance or induce predominantly proliferation of cells that produce homogeneous antibodies with the required degree of affinity. A method was proposed for rapid induction of low-dose tolerance by means of gradually increasing the concentration of antigen. There is validation of recommendations that increase the informativeness of some immunological studies.

The models of Bell [21-24] make it possible to describe a rather large set of immunological phenomena and, in the opinion of the author, this set can be enlarged even more with slight modification of the models, in order to predict the effects of carrying haptens of reproducing antigen, suppression of the response by passive antibodies, production of other classes of immunoglobulins, etc.

Some of the results obtained with Bell's models [21-24] can also be obtained from simpler hypotheses. Thus, the mode of an immune reaction developed by Soviet authors [16-20] consists of a system of 5 nonlinear differential equations describing the dynamics of change in concentration of precursor cells, B cells, plasmocytes, antigen and antibodies. The model is based on the assumption that processes of cell differentiation are regulated by their interaction with antigen, which occurs by the laws of biomolecular reactions. One contact with antigen is sufficient for the cell's state to be altered. The rates of the corresponding processes are proportionate to the product of cell concentrations multiplied by antigen concentration. The rate of proliferation of B cells is proportionate to $A/(c+A)$, where A is the concentration of free antigen and c is a constant, which causes inhibition of proliferation with large doses of antigen. The most comprehensive study of this model is reported in [18]. The model conforms well with the dynamics of the anamnestic response observed in real tests. It was also demonstrated that the intensity of the primary response depends on the dosage of antigen, and it has a maximum in the range of average doses. Its low intensity with small doses is attributable to weak stimulation of cells and with large doses, to rapid differentiation of precursor cells into B cells and "dead end" plasmocytes. The same work discusses a reduced variant of the model for the case of nonreproducing antigen, the total concentration of which in the organism was considered to be constant. A study of this modification of the model revealed that, in such a system, there can be a mode of immune response that is fluctuating and regressing, and it is correlated with experimental data on immunization of rabbits with protein antigen in adjuvant. This effect is attributed to feedback, with a lag of concentration of free antigen in relation to quantity of antibody-producing cells and antibodies.

Principles similar to those upon which Bell's models are based [21-24] were applied in the model of Bruni et al. [32-33]; however, the latter uses the continuous conception of heterogeneity of the population of immunocytes and antibodies involved in the immune response. The heterogeneous population is described by a continuous function of two arguments--affinity and time. The model is a system of five nonlinear integral-differential equations. In [34], the model of Bruni et al. was somewhat altered for the purpose of identification. The model was identified by the method of maximum plausibility, according to data from an experiment involving immunization of inbred guinea pigs with DNP-RNAase in complete Freund adjuvant. It was possible to evaluate, from the dynamics of concentration of antigen-bound antibodies, such parameters of the model as range of interval of share of antigen-bound immunocyte receptors in which there is stimulation of immunocytes for differentation and proliferation, constant rates of proliferation of immunocompetent cells and antibody production by these cells and plasmocytes. This study is a good illustration of the applications of the models for indirect evaluation of features that are difficult to measure in the immunity system and the immune response on the basis of easily measured parameters, for example, dynamics of concentration of bound antibodies in blood.

In the works of Jilec et al. [25-31], special attention was devoted to comprehensive consideration of the probabilistic aspects of interaction between antigen and lymphoid cells in the course of the immune response. The authors propose the following scheme of development of the immune reaction [25]. After the first contact with antigen, precursor cells are transformed into B cells, which divide several times. Upon second contact with antigen, the B cells change into plasmocytes, which produce antibodies for some time and then perish. The process of development of a clone originating from one precursor cell was modeled in a computer using the

Monte Carlo method. In subsequent works [26-28], a comprehensive study was made of stochastic models of processes of interaction between antigen and immunocytes. Studies were made of the distribution of density of probability of the moment of first contact of the cell with antigen and probability of at least one contact, provided that interaction of cells with antigen is a Poisson process. The obtained results are summarized if several contacts are required to stimulate the cells. Calculation is made of the number of offspring from one precursor cells that is formed in the organism after reimmunization, with exponential elimination of antigen from the organism. The effect of immunization as a function of antigen dosage and rate of its elimination is examined. Determination is made of optimum immunization method causing production of the maximum number of B cells.

2.2. Models With the Use of the T System

Development of immunology in the last 10 years revealed the inadequacy of Burnet's clone breeding theory [15] to describe mechanisms of the immunity system. Numerous data appeared on the role of T cells and macrophages in the immune response, which were reflected in works dealing with mathematical modeling [35-43]. The most comprehensive model consistent with current views [44] of the immunity system was developed by G. I. Marchuk and A. L. Asachenkov [40-41]. It consists of a system of 11 nonlinear differential equations describing interaction and dynamics of concentrations of such elements of the immunological reaction as T killers, T helpers, antibodies, IgM and IgG, T and B plasmocytes, macrophages, stem cells and antigen. The model also has a variable reflecting the rate at which antigen strikes the morbid organ. This model simulates a broad category of situations and processes related to the reaction of the immunity system to foreign antigen. By eliminating some elements or other, one can simulate immunodeficient states. The modeling results conform with clinical data, and they permit expounding a number of validated hypotheses concerning the characteristics of immunodeficiencies, for example, that the immune response is more sensitive to suppression of the T system than the B system, or that, in the case of a shortage of some elements, the existing ones increase in concentration to compensate for the absence of the former in the course of the response to an antigenic stimulus.

Mohler et al. [38, 39] propose a model of development of B and T cell clones, which is a system of nonlinear differential equations. Rendition of the system in a bilinear form makes it possible to submit the model to structural analysis.

The models in [36, 45, 46] differ somewhat from the one mentioned above, the former being based on the hypothesis of Jerne [35] that each antibody or cell receptor has antigenic properties causing the immune reaction of the organism to these antigens. In these works, emphasis is laid on interaction between different clones characterizing by mutually complementary structure of antigenic determinants, rather than on the mechanisms of development of different immunocyte clones. Simple conceptions of the form of interaction explain a wide range of immunological phenomena, such as tolerance of large and small doses, disruption of tolerance by cross-reacting antigens, tolerance of autologous antigens, interaction between systems of cellular and humoral immunity, suppressor and killer functions of T cells, memory and others, without going into the details of development of the clones themselves.

2.3. Simplified Models

It is difficult to make analytical studies of the behavior of models consisting of a system of nonlinear differential equations above the third order, while the

results of solving such systems on a computer are rather difficult to interpret. For this reason, many authors use simplified models of the integral immunity system in order to use, for analysis thereof, powerful methods of studying differential equations in the phase plane [16, 18-20, 47-58]. This approach does not take into consideration the fine points of mechanisms of the immunity system, but it does consider the main cause and effect relations between the quantity of pathogenic agent in the organism and intensity of the immune response, which makes it possible to conduct a qualitative analysis of the dynamics of such a system and demonstrate the main possible types of its behavior. In some cases [49-51, 54] this permitted formulation of recommendations with regard to therapeutic tactics.

Thus, models obtained with the use of Bell's simplified models [21-24] were discussed by Bell and Pimbley [55, 56-58]. Simplification is obtained because the details of proliferation and differentiation of the lymphocyte clone are not taken into consideration in the models. Clone dynamics are described by one variable--the concentration of lymphocytes capable of producing antibodies [56]. The model consists of a system of three nonlinear differential equations describing the dynamics of concentration of reproducing antigen, immunocytes and antibodies, the appearance of which resembles the predator-prey model of Volterra [59]. There was formulation of conditions of existence and uniqueness of the positive stationary point and the range of resistance for various proportions of parameters was indicated as a result of comprehensive theoretical analysis of the model [56]. A classification was made according to nature of resistance of stationary points in three-dimensional phasic space. Studies were made of the points of bifurcation of periodic solutions. Stable fluctuations in the system, stable stationary states and trajectories directed toward them are interpreted as instances of antigen invasion under the control of the immune system, while other types of solutions are interpreted as uncontrolled development of disease.

Bell [55] describes a reduced variant of this model, in which only two elements of the reaction are considered--antigen and antibodies. As a result of theoretical studies of this variant [56-58], it was proven that there is a closed separatrix and the conditions were described under which the solution forms a stable or unstable finite cycle. By using the results of theory of bifurcation of dynamic systems on a plane, the author proved the existence of periodic solutions with wide amplitudes branching away from the separatrix.

Conceptions of models similar in basic principles are developed in the works of Yu. M. Romanovskiy et al. [16], O. A. Smirnova [18-20]. These authors demonstrated that, depending on the parameters (such as rate of reproduction and flushing out of antigen) and initial conditions (for example, initial dose of antigen), various modes may appear in the system: periodic fluctuations; arrival of the system at a stable equilibrium characterized by low concentrations of all components; unlimited growth of antigen concentration. These modes are interpreted in the same way as in the works of Bell and Pimbley [55-58]. They are related to the periodic course of infectious disease, recovery and death of the organism. It was noted that the presence of fluctuations in such systems could have been expected, since there was feedback with the delay which is referable to the following chain: antigen concentration--cell proliferation--antibody synthesis--antigen concentration. In the model that does not deal with the dynamics of immunocytes [55], an analogous effect is achieved by interaction between antibodies and antigen on the predator--prey principle.

As noted in several works [16, 18-20], one of the substantial distinctions of the immune system determining the dynamics of its reactions is the element of delay in the feedback chain. The delay effect was investigated comprehensively by B. F. Dibrov et al. [47-54]. The models proposed by the authors are systems of two or three nonlinear differential equations with a delayed argument for the rates of change in concentrations of immunocytes, antibodies and antigen, depending on the concentrations of the same elements in the organism at prior times. A study conducted by the authors revealed that many of the above-mentioned modes of dynamic behavior of the system (fluctuation, destruction of antigen, unlimited growth in quantity thereof, etc.) can be obtained by altering the magnitude of delay. One of the most important parameters determining the mode of the reaction is the lag in antibody production. With a small delay there can be stationary coexistence of antigen and antibodies.

As a result of studying the models, the authors formulated recommendations on the optimum tactics for using antibiotics and serum to completely destroy antigen in the body and prevent a recurrence of disease.

Analysis of the simplified models mentioned in this section was not associated with quantitative comparison of the results of modeling to studies of a living organism. Nor could this be demanded because of the great simplification of the models. The value of this approach consists of the fact that it does not require excessive details of phenomena and provides the opportunity to gain deeper knowledge about their causes and mechanisms on the qualitative level, which could suggest to the researcher the required direction for development of more detailed and adequate models. Moreover, the simplified models clarify some effects inherent in the immunity system, which occur whatever the amount of details in the description. We refer, for example, to the delay effects, relationship between rates of reproduction of components of the immune system and antigen and the form of dynamic behavior of the system, etc.

2.4. Difficulties and Prospects of Development of Models of the Integral Immunity System

The above discussion of studies of models, dealing with analysis of the intrinsic mechanisms determining the dynamics of development of the overall immune response demonstrated the possibility of using models to study the essence of immunological phenomena, to evolve validated desires and recommendations for biological research, to choose optimum therapeutic tactics, check the theoretical predictions and obtain corollaries from the postulates and hypotheses serving as the basis of the model.

The flaws of models [16-34] based on Burnet's clone-breeding theory include the absence of current conceptions of involvement of the T system and macrophages in the immune response. However, such models can be used to simulate the reaction of the immunity system to T-independent antigens. Moreover, in the course of developing the models, the authors found some useful procedures and methods of formalizing immunological phenomena, which can be used in the future in the design of more detailed and accurate models.

The models that include the T system [35-43] are closer to reality, but they also could be refined and modified with consideration of the latest data on the immunity system. This situation with modeling is attributable to the specifics of the subject of investigation, the immunity system, which refers to the relatively rapid

variability and occasionally contradiction of opinions concerning the principles and mechanisms of its function. In the situation where several mutually exclusive hypotheses are used to explain the same phenomenon, the feasibility of rapidly checking the hypotheses with mathematical models is particularly valuable. In such cases, the following features of models acquire much importance: flexibility, capacity for easy modification and inclusion of new conceptions and mechanisms. The possible means of obtaining these features are to have a modular construction of the models and execution of the models in a general form that permits parametric input of a broad range of immunological "scenarios" for simulation purposes [60-62].

3. Models of Individual Immunological Phenomena

The method of mathematical modeling is used effectively, not only to examine whole immunological reactions, but to analyze the details of immunity system function and different aspects of interaction of antigen with its components, which is done both in vivo and in vitro.

3.1. Models of Immunological Phenomena in a Living Organism

The element in common in the studies discussed in this section is that authors used the model method for quantitative descriptions and analysis of some specific process or unit of the immunity system in order to investigate their mechanisms. The results of such studies can be well-used to design models of the entire immunity system.

These studies can be classified in three groups according to their directions. The first includes works containing theoretical constructions occupying an intermediate place between analysis of data based on regression methods and the model approach [63-71]. They try to define the functional relations interpolating the functions obtained in biological studies. The second direction refers to models of single pathological processes [18, 72-84], and the third is related to analysis of the function of different elements of the immunity system and different situations [85-90] that arise in the course of biological studies.

The cycle of works by M. I. Levi et al. [63-68] demonstrated that the instant amount of plasmocytes in a regional node during a response is proportionate to the logarithm of the immediate concentration of antigen (antigen is introduced at zero time and its quantity diminishes exponentially thereafter).

In models of pathological processes such as neoplasmosis [82-84], tuberculosis [73, 74], malaria [72], autoimmune reaction [18, 75], abscess [76, 77] and chronic forms of viral diseases [78-81], various forms are demonstrable in the behavior of the system under study, which are related to the correlations between parameters of the model, which makes it possible to offer recommendations concerning optimum tactics in treatment of the disease. For example, the model of malaria [72] is a system of nonlinear differential equations describing the dynamics of concentrations of healthy and infected erythrocytes, merozoites, plasmocytes and antibodies in the organism. The authors demonstrated that cyclic modes are possible in this system, i.e., autofluctuations at the frequency of the malaria attacks. Calculation was made of the parameters of reactions with which unstable modes are observed, which are interpreted as death or recovery of the organism. Chronic viral disease has been interpreted [78-81] as a stationary state of an immunological process, and there was mathematical validation of a method of treating chronic diseases with additional amounts of the pathogenic agent and exacerbation of the disease.

The quantity of plasmocytes as a function of dosage of mixture of lymphocytes injected in the organism was obtained with a model of interaction of B and T lymphocytes under experimental conditions in an in vivo cell culture [85]. The results of modeling conformed well to the results of biological studies and make it possible to estimate the share of B and T cells in the mixture used.

Compartment models of proliferation and differentiation of cells in the thymus [86-88] make it possible to simulate normal development of the thymus, postradiation recovery thereof and degeneration at the advanced stage of life, as well as to analyze the effects related to development of the vascular system, which are involved in nutrition of thymocytes [87, 88]. Analysis of the model yields a number of interesting conclusions about processes in the thymus. For example, there was validation of the conclusion that during differentiation of cells of maximum size into cells of a smaller size about 5% of the cells that mature return to the parental pool [86]. An analogy was noted between this process and function of amplifier with positive feedback.

The compartment method was also used to simulate processes of lymphocyte circulation in the organism [90] and passage thereof through different parts of the spleen [89]. Such models can be used to simulate and interpret studies with the use of labels, as well as to calculate the actual concentrations of components in different organs and parts of the body involved in the immunological reactions. Moreover, it is possible to evaluate changes in concentrations of these components under the influence of factors that alter the intensity of lymph flow, for example weightlessness and hypodynamia, which are space flight factors.

3.2. Models of in Vitro Immunological Reactions

For purposes of studies of processes in vitro, there are models of precipitation and agglutination [23, 91-104], reactions of antigen with antibodies and cell receptors [7-14, 23, 105], plaque formation and lysis of erythrocytes in the presence of complement [106-120], virus neutralization [121-125] and phagocytosis of foreign particles [126, 127]. The theoretical constructions submitted in most of these works are valid for both in vitro and in vivo reactions.

Aladjem and Palmiter discussed in the most general form the phenomena of precipitation and agglutination [94]. They expounded a theory of interaction of heterogeneous population of bivalent antibodies with polyvalent antigen and proposed a recursive procedure for determining the correlation between the function of probability distribution density of antibody affinity and quantity of precipitate and soluble components in solution. Special instances of this phenomenon are discussed in [96, 97, 101].

The process of precipitation and agglutination was studied comprehensively by De-Lisi [100]. The theory expounded by this author predicts the presence of a critical ratio between reactants separating the areas of strong and weak aggregation. This ratio is viewed as a function of valency of antibodies and antigen, degree of their heterogeneity, and it depends on the effects of intramolecular reactions. The author obtained ratios between number of antigen molecules in the mixture and quantity of bound antibodies, as well as between quantity of antibodies and number of antigen molecules in large aggregates.

Theory of the precipitation phenomenon in the case of flat concentric immunodiffusion in agar is expounded in the works of Aladjem et al. [91-93, 95]. By solving the classical equation of diffusion, these authors succeeded in finding a link between the coordinates of the precipitation zone and time required for appearance of the zone, as well as between the coefficients of antigen and antibody diffusion and the slope of the precipitation zone; they also were able to calculate the concentrations of antigen and antibodies at any point of the plane at any point in time.

Crothers and Metzger [105] analyze the possibility of defining avidity in terms of statistical mechanics, which clarifies the role of molecular structure in antigen--antibody reactions. Goldstein [106], who used the thermodynamic approach to calculation of magnitude of affinity and effective valence of IgM under different conditions and took into consideration the known data from biological studies, concluded that the valence of IgM is related not only to concentration of hapten (at high concentration valence equal 10 and at low, 5), but to the force of interaction between antigen-binding centers of IgM, as well as width of distribution of serum affinity. A wide distribution of affinity leads to a valence of 5, even when there is no interaction between centers.

In the cycle of works submitted by De-Lisi et al. [110-117] and several others [106-109, 119], theory of kinetics of formation of hemolytic plaques under different conditions is expounded: in media differing in dimensionality [114], with inhibition of plaque production by hapten and polyvalent antigen [106, 111, 112], in the case of IgM-synthesizing cells, etc. The typical means of formalization is the description of plaque kinetics with a system of differential equations, including the equation for diffusion of antibodies from a point source--plasmocyte and equation of chemical kinetics of the reactions between antigenic determinants and active antibody centers. The authors obtained expressions that link the characteristics of plaques (radius, growth rate, number of plaques) with the magnitude of antibody affinity, rate of secretion of the latter by plasmocytes, concentration of components that inhibit the reaction. For example, it was demonstrated that the largest plaques are formed when there is a certain average level of affinity, and with increase in overall concentration of antigenic determinants there is a decrease in affinity of antibodies forming the largest plaques [114]. In the case of high density of hapten on erythrocytes, the appearance of the differential curve of intensity of inhibition of plaque-producing reaction as a function of amount of hapten reflects the distribution of affinity of antibodies for hapten--distribution of rate of antibody secretion by plasmocytes [106, 111, 112]. The authors' comprehensive study increased substantially the informativeness of widely practiced tests that make use of plaque production, and its results should be taken into consideration in planning and performing such experiments.

The approach used in the above-mentioned works, which is based on the description of random interaction between components according to the laws of bimolecular reaction, is also used for analysis of interaction between polyvalent antigen and immunocyte receptors [7-14, 23], as well as antibodies and antigenic determinants on the surface of viruses [121-125]. Modeling of the process of formation of a grid of receptors, which are cross-linked with polyvalent antigen, on the surface of B lymphocytes demonstrated the possibility of controlling the rate of formation of this grid by means of level of affinity, even in the case where the bonds between antigen and receptors are irreversible. The process of grid formation, particularly for highly affine receptors, can be effectively inhibited by free hapten, although hapten does not compete with polyvalent binding in equilibrium. These studies

stress once more the importance of quantitative measurement of number of receptors and their mobility on membranes, as well as kinetics of antigen binding with immunocytes, in order to comprehend the mechanisms of clone breeding and other aspects of immunological reactions.

Thus, our analysis established that models of different immunological phenomena conform better to the results of biological studies than models of the entire immune response, and they provide concrete quantitative data that can be put directly to practical use. This can be easily explained by the possibility of simpler and more accurate description of a separate phenomenon than a system as a whole, more accurate formulation of assumptions and simplifying hypothesis, with consideration of which the model was constructed on the physical level of strictness. Obviously, it would be impossible to advance further with mathematical modeling without developing mutually complementary models of both types.

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EXPERIMENTAL AND GENERAL THEORETICAL RESEARCH

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STATUS OF COSMONAUT BIFIDOFLORA BEFORE AND AFTER SPACE FLIGHTS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 14-18

[Article by G. I. Goncharova, N. N. Liz'ko, A. M. Lyannaya, V. M. Shilov, T. I. Spitsa, G. D. Syrykh and V. A. Kazantsev, submitted 3 Feb 79]

[English abstract from source] The state of bifidoflora was examined in eight cosmonauts before and after space flights of varying duration. Prelaunch quantity of bifidobacteria decreased drastically. In space flights of 30 days and longer the level of acid formation by bifidobacteria was reduced. The species composition of bifidoflora remained stable. The most typical intestinal species of bifidobacteria were B. longum and B. adolescentis.

[Text] Man's presence in an altered habitat, with different diet and exposure to stressors could have an effect on microflora of the intestine. Biological isolation of man in itself leads to impairment of normal ecological proportion of different elements of intestinal microflora, manifested by a drastic decrease in or disappearance of some of its representatives [1]. Studies of fecal microflora of individuals who had spent time in a sealed compartment revealed a dysbiotic type of change: disappearance of drastic decrease in bifidobacteria and lactobacilli, impaired quantitative proportion of bifidobacteria and E. coli. Bifidobacteria react the most rapidly and sensitively to adverse conditions [3]. Changes in bifidoflora reflect the very earliest changes in intestinal microbiocenosis, which occur long before clinical manifestations in response to extreme factors. For this reason, some researchers consider bifidobacteria to be an indicator of the status of the macroorganism. The need to study this group of bacteria in cosmonauts is unquestionable [4]. It is considered quite important and urgent to determine not only quantitative, but qualitative changes in the profile of bifidoflora, as well as to study the biological properties of bifidobacteria that have been submitted to space flight factors and to compare them to analogous parameters of bacteria isolated in the preflight period.

In this article, we submit the results of a quantitative and qualitative study of the bifidoflora of 8 cosmonauts before and after 5-8-day orbital flights aboard Soyuz-13 and Soyuz-19 spacecraft, as well as 30- and 63-day flights aboard the Salyut-4 orbital station, and of three subjects in a control group.

Methods

We made a dynamic study of the cosmonauts' bifidoflora in the preflight period (45, 30, 21, 15 and 7 days prior to the flight), the prelaunch period (2-3 days

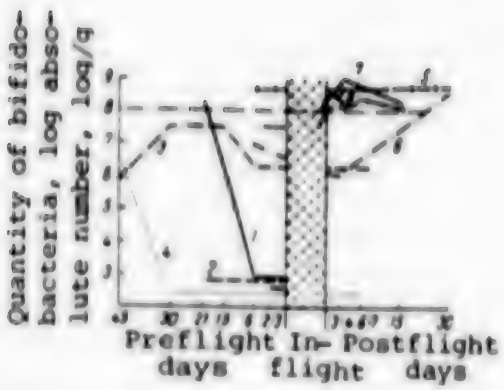
before the flight), immediately after returning to earth, then 3-4, 7, 15 days and 1 month after landing. A solid nutrient medium with Na azide was used for quantitative assay of bifidobacteria per gram feces and subsequent isolation of cultures. We used our modification of the method of application of watch glass [5]. The concomitant microflora was removed from the strains [6, 7] to study the biological properties of bifidobacteria. The isolated bifidobacterial cultures were reinoculated into liver broth, which we modified, for accumulation of biomass and cultured at a temperature of 37.5°C for 24-48 h [8]. The bacterial cells were separated by centrifuging at 3500 r/min, the supernatant was decanted, the sediment resuspended in saccharose-gelatin medium, decanted into vials, with 1 mℓ in each, and lyophilized. The sealed vials with dried strains were stored at a temperature of 4-6°C. In all, we purified and lyophilized 366 strains of bifidobacteria, 175 of which were isolated before flights and 191 after. Morphology and acid-producing activity was studied in 366 strains; bifidobacteria were identified and species determined in 118 strains, and nucleotide composition of DNA was determined in 3 strains. We used the light optic method to study morphology of the strains, and tested acid-forming activity after 6, 16, 24, 32, 48, 56, 72 and 96 h of cultivation in liver broth. Determination was made of overall acidity (quantity of acids produced by a strain in 10 mℓ nutrient medium) by the method of titration with NaOH decinormal alkali. Phenolphthalein served as the indicator. The experiments were set up using our modification of the method of Reuter [9, 10]. The species of bifidobacteria was identified according to fermentation of 10 carbohydrates and alcohols--arabinose, xylose, mannose, cellobiose, lactose, inulin, mannitol, sorbitol, inositol and salicin. We studied the nucleotide composition of bifidobacterial DNA by the method of paper chromatography combined with ultraviolet spectrophotometry [11].

Results and Discussion

Our studies demonstrated quantitative changes in bifidoflora of cosmonauts in the preflight period. Only 3 out of 11 subjects examined presented $6.4\text{-}8.2 \cdot 10^8$ bifidobacteria per gram feces. In 4 cases (both cosmonauts of the Soyuz-13 spacecraft, commander of the 63-day mission aboard Salyut-4 orbital station and flight engineer of Soyuz-19 spacecraft) failed to demonstrate bifidobacteria even in a dilution of 10^{-4} 30 and 21 days before the flight. Bifidoflora was demonstrable only in dilutions of 10^{-6}-10^{-7} 2-3 days before lift-off, and it was 100 times lower in the commander of Soyuz-19, 10 times lower in flight engineers of the first and second missions aboard the Salyut-4 orbital station (see Figure).

The Figure shows that the decrease in bifidobacteria was the most marked just prior to the flight in 7 out of 8 cosmonauts (participating in flights of different duration). At this time, the level of bifidoflora was below the normal range (shown by wavy line on Figure), which warranted the assumption that nervous and emotional tension had an effect in the prelaunch period.

In the postflight period, bifidoflora was restored to the level inherent in healthy people in two out of four cosmonauts (participating in short-term flights). This indicates that the low level of bifidoflora on the eve of the flight is due to nervous and emotional stress. Elevation of bifidobacterial level in cosmonauts involved in the 63-day flight is related, in our opinion, to the set of preventive measures used on board, in particular, intake of vitamin and amino acid supplements. The bifidoflora level was stable in one cosmonaut. We believe that the quantitative changes in bifidoflora content were attributable to neuroemotional tension preceding the space flight.



Bifidoflora of cosmonauts in preflight and postflight periods.
X-axis, time of examination; y-axis, quantity of bifidobacteria, log absolute numbers.

1-4) change in quantity of bifidobacteria in preflight period, CDR (1) and FLE (2) of Soyuz-13, CDR (3) and FLE (4) of Soyuz-19

5-8) postflight changes in quantity of bifidobacteria in CDR (5) and FLE (6) of first mission, CDR (7) and FLE (8) of second mission aboard Soyuz-4.

Wavy line shows bottom range of normal bifidoflora content

It is known that the autoflora is a sensitive indicator of various changes in general reactivity of the body. Diverse environmental factors, which affect neuroregulatory mechanisms of the integral organism, are reflected in quantitative and qualitative composition of autoflora [12].

Recently, data have been obtained, which are indicative of reliable changes in intestinal microflora composition in the presence of complex nervous and emotional stress. Disturbances of intestinal biocenosis are manifested by a decrease or disappearance of bifidobacteria and lactobacilli [3, 4, 13]. In addition, there is information indicative of changes in composition of autoflora in essentially healthy people during periods of intensive training and deep diving [14].

For this reason, there are grounds to interpret the changes in bifidoflora in the preflight period as the result of the effect of nervous and emotional tension during the period of training and preparing for flights. It should be noted that the changes in autoflora occur much earlier than clinical symptoms [15], which was confirmed in the clinical examination of cosmonauts in the preflight period, when there were no complaints or deviations from normal.

However, the decline of level of bifidoflora led to changes in the aerobic part of the intestinal microbiocenosis, manifested by an increase in its percentile content in the overall biocenosis, quantitative growth of such of its representatives as staphylococci, E. coli (lactose-negative or with diminished fermentive activity), Proteus, etc.

One would think that the lability of bifidoflora in the preflight period could determine, to some extent, the changes in microbial cenosis during space flights.

Morphological studies of isolated bifidobacterial strains confirmed the polymorphism inherent in this genus of microorganisms. In smears, we demonstrated simultaneously bacilli with bifurcation at the ends, club-shaped ones, rods with thickening in the middle, spherical thickening at the ends and others. In solid medium, the form of the bifidobacterial colonies resembled buckwheat grain and in liver broth, it resembled a comet or nail. We failed to demonstrate appreciable morphological differences between strains isolated from cosmonauts before and after flights.

All of the strains were active acid producers, and they produced acids in liver broth starting in the 6th-8th h of cultivation. By 24-48 h, there was the most vigorous increase in acids, and subsequently (by the 72d-96th h of cultivation) if there was increase in acid production, it was insignificant. We failed to demonstrate changes in dynamics of acid production by strains isolated after the flights, as compared to the strains isolated in the preflight period; however, there were some changes in quantitative level of produced acids. Thus, we observed a tendency toward diminished vigor of acid production in strains isolated immediately after the flight in 4 participants of 30- and 63-day flights aboard the Salyut-4 orbital station. There was a decrease in number of strains producing large amounts of acids, as compared to the preflight period.

Immediately after returning to earth, the CDR [commander] of the second mission aboard Salyut-4 presented 2 strains that acidulated the nutrient medium to 67-73°, according to Turner. No strains with such low vigor of acid production were isolated in the preflight period and 7, 15 days after the flight.

With regard to the FLE [flight engineer] of the second mission aboard the Salyut-4 orbital station, 15 strains out of 23 acidulated the culture medium to 120° according to Turner before the flight and only 3 out of the 37 isolated strains did so after the flight.

Both cosmonauts of the first mission aboard Salyut-4 had strains with high energy of acid production (130° according to Turner) before the flight, while not a single analogous train was isolated immediately after the flight. This is quite interesting, and it is necessary to continue the studies of biological properties of bifidobacteria isolated from participants of long-term space flights.

Identification of bifidobacteria revealed that the species, B. longum, was the most widespread in cosmonauts. It was isolated from 8 people, in 5 of whom (both cosmonauts of Soyuz-13, CDR of Soyuz-19 and 2 subjects in the control group) no other species were demonstrated.

The typical species for this group was also B. adolescentis, which was found in 5 people, only 2 of whom presented only this species. Only one species of bifidobacteria was found in the intestine of 7 subjects, 2 (CDR of first mission aboard Salyut-4 orbital station and FLE of second mission aboard Salyut-4) had 2 species (B. longum and B. adolescentis) and the FLE of the 30-day mission aboard Salyut-4 presented 3 species (B. longum, B. adolescentis and B. bifidum).

We observed stability of species representation in the same subject over a period of 1.5 years (duration of observation period). For example, bifidobacterial referable to the B. longum species were isolated from the CDR of the 63-day mission aboard Salyut-4, and 2 species were isolated just as consistently before and after the flight, B. longum and B. adolescentis, from the FLE. However, even with such close contact for many days, we failed to demonstrate settling of B. adolescentis in the intestine of the CDR.

The observed changes in physiological properties of bifidobacterial strains in participants of long-term flights prompted us to check whether long-term space flights caused changes in nucleotide composition of DNA.

We obtained data on nucleotide composition of DNA of three strains of bifidobacteria: 2 strains were isolated before the flight and 1 immediately after the

cosmonaut returned to earth after 63 days aboard the orbital station. All 3 strains were referable to the strongly GC [guanine-cytosine?] type with coefficients of specificity of 1.6, 1.61 and 1.62. The molar percentage of GC in DNA of all strains did not differ from parameters inherent in the genus Bifidobacterium, constituting 61.5, 61.8 and 62.0. Preliminary data revealed that the nucleotide composition of DNA does not change in strains isolated from cosmonauts before and after long-term space flights.

Thus, the results of our studies indicate that nervous and emotional stress in the preflight period leads to drastic reduction of bifidobacterial content and changes in aerobic flora of the cosmonauts' intestine. Space flights lasting 30 or more days cause a decrease in acid-producing activity of bifidobacteria.

It was established that B. longum and B. adolescentis are the most typical bifidobacteria of the intestine. Stability of species composition of bifidoflora in the same individual was observed over a 1.5-year observation period.

The obtained findings are of practical importance to development of effective biologicals-eubiotics, for normalization of the intestinal microflora during the period of preflight cosmonaut training and in the course of long-term space flights.

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RESULTS OF STUDIES OF HEMODYNAMICS AND PHASE STRUCTURE OF THE CARDIAC CYCLE DURING FUNCTIONAL TEST WITH GRADED EXERCISE DURING 140-DAY FLIGHT ABOARD THE SALYUT-6 STATION

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[Article by A. D. Yegorov, O. G. Itsekhovskiy, A. P. Polyakova, V. F. Turchaninova, I. V. Alferova, V. G. Savel'yeva, M. V. Domracheva, T. V. Batenchuk-Tusko, V. G. Doroshev and Ye. A. Kobzev, submitted 29 Feb 80]

[English abstract from source] During the 140-day flight of the orbital station Salyut-6 two primary crew members performed 5 exercise tests on a bicycle ergometer at a load of 750 kg-m/min for 5 min. During tests heart rate, and before and after tests arterial pressure, left ventricular chronograms and cardiac output (rheographically) were recorded. In comparison to the preflight tests, the flight tests were characterized by less expressed changes in phasic parameters, moderate increase in cardiac output and, occasionally, insufficient decrease in peripheral resistance. These changes can be attributed to the weightlessness-associated deficiency of the circulating blood volume.

[Text] Diminished physical fitness of cosmonauts is observed in most cases in the postflight examination [1-3]. Data were obtained during the flight aboard the Salyut-1 station indicative of some increase in changes in circulatory parameters under the influence of exercise [4]. These phenomena were related to development of signs of deconditioning of the cardiovascular system under the influence of weightlessness. At the same time, the overall reaction of the circulatory system to exercise during in-flight tests did not differ essentially from the preflight reaction of crew members of the Salyut-4 and Skylab stations; however, after returning to earth the cosmonauts presented a substantial decrease in endurance of physical loads [5, 6]. Our objective here was to continue with accumulation of data pertaining to the process of man's adaptation to long-term weightlessness and to assess the fitness of cosmonauts on the basis of the reaction of the cardiovascular system to graded exercise. The data obtained in the course of the flight were interesting in view of extension of duration of the flight to 140 days and increase in volume of preventive physical training.

Changes in hemodynamic parameters of second crew of the Salyut-6 orbital station related to test with GPE before and during the flight

Parameter	Conditions	CDR preflight	CDR in-flight days 29	61	87	119	FLE preflight	FLE in-flight days 29	61	87	119
HR, per min	bv	66 (64–68)	68	74	67	86	59 (56–61)	61	66	69	73
	load	118 (116–120)	117	135	129	140	108 (103–115)	109	112	115	115
	rp	92 (91–95)	77	83	93	120	85 (80–91)	88	80	103	—
MAP, mm Hg	bv	69 (66–72)	60	61	65	68	62 (59–64)	60	60	66	68
	rp	73 (68–80)	70	73	75	68	66 (60–69)	58	67	72	—
AAP, mm Hg	bv	90 (88–92)	86	78	84	90	87 (78–88)	88	90	84	88
	rp	98 (92–105)	92	90	98	98	84 (90–100)	104	82	93	—
LSAP, mm Hg	bv	104 (102–106)	96	86	100	99	105 (97–110)	100	86	107	96
	rp	119 (110–132)	115	100	112	104	112 (104–121)	118	96	103	—
ESAP, mm Hg	bv	132 (129–139)	123	134	128	130	136 (124–143)	142	138	144	139
	rp	154 (147–166)	148	155	140	143	158 (146–180)	165	156	150	148
SV, ml	bv	115 (101–148)	121	128	89	122	153 (146–190)	163	172	150	186
	rp	150 (132–168)	180	128	108	128	193 (182–243)	178	198	167	190
MV, l/min	bv	7.6 (6.4–9.1)	8.1	9.5	6.7	8.3	9.4 (9.2–12.8)	9.6	11.5	11.0	12.8
	rp	13.8 (12.0–15.8)	13.3	14.0	11.6	12.6	16.7 (15.8–20.4)	16.7	18.4	15.7	19.6
SPR_a, arbitrary units	bv	23.5 (17.6–28.0)	20.9	16.1	23.2	19.9	18.9	18.1 (11.9–18.6)	17.9	13.6	15.1
	rp	15.5 (15.3–15.7)	13.6	12.6	—	15.3	14.9	11.4 (8.4–12.3)	11.9	8.7	11.4
SPR_a/SPR_n, %	bv	105 (96–108)	101	99	93	79	106	102 (92–104)	104	94	100
	rp	119 (114–124)	108	106	—	115	115	114 (106–118)	120	96	108
PW_a, cm/s	bv	638 (591–710)	750	806	701	750	686	572 (523–629)	652	571	613
	rp	804 (736–900)	764	843	800	844	1000	667 (521–705)	643	—	702
IC, ms	bv	60 (60–61)	46	68	37	46	44	61 (60–63)	48	37	45
	rp	60 —	29	37	43	37	30	47 (45–50)	37	—	45
PE, ms	bv	284 (278–290)	321	275	290	294	253	280 (270–290)	313	303	283
	rp	210 (185–235)	290	235	254	250	206	222 (200–240)	275	—	238

Key: bv) initial values before test
load) maximum value during test
rp) values for first min of recovery period (range of fluctuation shown in parentheses)

Methods

The test with graded physical exercise (GPE) was performed 2-3 times in the preflight period, on the 29th, 41st, 62d, 97th and 119th days of flight. The cosmonauts worked on a bicycle ergometer, with pedaling force of 750 kg-m/min for 5 min. We recorded the following: electrocardiogram in the DS lead throughout the test; before and after the test--rheogram with circular electrodes placed on the upper third of the arms, kinetocardiogram from the region of the apical beat, sphygmogram of the femoral artery in the upper third of the thigh and tachooscillogram of the brachial artery. The obtained information was transmitted via telemetry channels to earth. Data processing included determination of heart rate (HR), stroke (SV) and minute (MV) blood volumes, minimum (MAP), average (AAP), lateral (LSAP) and end systolic (ESAP) and pulsed (PAP) arterial pressure (AP), rate of propagation of pulse wave over the aorta (PW_a), duration of phase of isometric contraction (IC), period of ejection of blood by the left ventricle (PE), IC/PE ratio, actual (SPR_a) and nominal (SPR_n) specific peripheral resistance. We estimated SV with the formula of A. A. Kedrov [7], the parameters of AP by the method of N. N. Savitskiy [8] and duration of phases of the cardiac cycle by the method of L. B. Andreyev [9] as modified by V. A. Degtyarev [10]. We compared the severity of reactions of the cardiovascular system to the in-flight functional tests to the reactions in ground-based tests, which were considered to be the control (see Table).

Results and Discussion

The cosmonauts did not complain of poorer well-being during performance of the GPE test.

The deviations from levels of planned exercise did not exceed ±6% in most of the in-flight tests. Overall work (in 5 min) was somewhat greater than the nominal in the commander (CDR) on the 97th and 119th days (by 10 and 31%, respectively), and in the flight engineer (FLE) on the 119th day (by 9%).

During most of the flight tests, HR was initially higher than on earth. During exercise, HR of the CDR was above the preflight level, reaching 123-140/min (the maximum being 120/min before the flight), in all of the flight tests, with the exception of the one on the 29th day. HR did not exceed the maximum preflight level in any of the flight tests on the FLE. The increment of HR, in relation to initial level, did not exceed preflight values in either the CDR or FLE. The ratio of total number of cardiac contractions to total work (for all 5 min of pedaling) was either lower in the flight tests (29th, 62d and 119th days) than preflight values, or else was virtually the same, which was indicative of preservation of an adequate HR reaction to exercise, in spite of some deviations in its performance. Development of a steady state was usually observed in the 2d-3d min of exercise, and duration of the flight did not affect the nature of "getting warmed up." Restoration of HR after the test occurred just as it had in the ground-based tests. The only exception was the test on the 97th in-flight day, when HR of the CDR in the 5th min of the recovery period exceeded the initial level by 13 beats/min.

On the whole, the parameters of AP in the 1st min after the test did not differ from preflight findings. Deviations were demonstrated in the CDR, in the tests performed on the 29th, 41st and 97th days, when MAP increased by 10-12 mm Hg (the preflight maximum was 8 mm Hg), and in the FLE in the tests performed on the 29th and 62d days, when the increment of LSAP constituted 18 mm Hg (versus the maximum of 11 mm Hg before the flight). There was somewhat slower recovery of AP in the

CDR during tests on the 41st day and FLE on the 29th day, as compared to findings on the ground. The changes in blood volumes recorded after the tests either failed to differ from preflight values, or were the least marked. While the increment of MV in response to the exercise constitu ed 101-109%, in flight it was in the range of 39-77%. Typically enough, throughout the flight the increase in SV was less marked than on the ground. Maximum increment of SV in the flight tests did not exceed 17-27% (it reached 18-65% in the preflight tests), whereas during the second half of the flight the fluctuations ranged from +5 to -2%. The decrease in SPR_n and SPR_a during the flight period immediately after the test never exceeded preflight levels; however, the decrease of SPR_a in tests on the 41st and 97th day were less marked than SPR_n in the CDR, which was indicative of inadequate carrying capacity of arteriolar sphincters.

The compensatory increase in PW_a in response to exercise conformed with preflight findings in most of the in-flight tests. The only exception was a somewhat greater increment of this parameter in the CDR on the 62d day (25%, versus the maximum of 14% before the flight).

In both cosmonauts, the changes in phasic structure of the cardiac cycle immediately after the test were manifested in the form of the phasic syndrome of hyperdynamia (according to V. L. Karpman [11]); however, the shortening of IC was less marked in flight: by 0.008-0.017 s, versus 0.018-0.021 s before the flight. In tests that the cosmonauts performed on the 62 day, this time interval did not change in the FLE, and in the CDR it even became 0.006 s longer. Shortening of PE was either similar to the preflight findings (in the FLE) or less marked (CDR). In most cases, IC/PE diminished to the same extent as in preflight tests. A more significant decline of this parameter was demonstrated in the CDR on the 29th day (by 35%, versus 19% before the flight). The 62d flight day was an exception, when IC/PE increased by 19-42% in both cosmonauts.

Thus, the reaction of the cardiovascular system to GPE in flight presented some differences, as compared to the preflight reaction. This was manifested by a less marked phasic syndrome of hypodynamia (mainly due to relatively minor changes in IC), moderate increment of MV and increase in SPR_a/SPR_n ratio.

Evidently, we can relate these changes in hemodynamics and phasic structure of the cardiac cycle to the fact that, in weightlessness, there is approximately a 300-500 ml decrease in circulating blood volume due to development of general dehydration of the organism [12]. This was indicated with some degree of certainty by the fact that there was a weight loss and decrease in volume of the lower leg of the cosmonauts [13]. The hypothesis had been previously expounded that hypovolemia in flight affects the reactions to functional exercise tests. The shortage of circulating blood should apparently affect, first of all, the intensity of venous return and, as a consequence, cardiac output. The physical load and, particularly, the start of the recovery period are characterized by deposition of part of the blood in the capacitive vessels of functioning muscles [14]. In weightlessness, this process apparently leads to a more critical situation, since the circulating blood volume is low to start with. Maintenance of cardiac output under such conditions should occur chiefly by means of intensification of chronotropic influences on cardiac function, with relatively minor increment of SV [15]. Indeed, according to the results of in-flight GPE tests, such a tendency was demonstrable, particularly during the second half of the flight. Concurrently there were relatively slight changes in the contraction phase of the myocardium. Alteration of the phasic structure of the

cardiac cycle was apparently indicative of circulatory volume deficiency of the heart right after completing the DPE, as well as rapid restoration of initial level of venous return of blood to the heart due to triggering of compensatory vascular mechanisms. The fact that, in some cases, we demonstrated a difference between SPR_a and SPR_n, as well as more marked increment of AP and PW_a, is indicative of an increase in arterial vascular tonus, which compensates for the diminished volume of circulating blood.

In conclusion, it should be noted that the dynamics of circulatory parameters during the tests with GPE in both crew members were generally indicative of the absence of in-flight overt signs of physical deconditioning. Apparently, this was aided by the intensive physical training that the cosmonauts practiced throughout the entire 140-day flight.

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UDC: 612.745.6:[612.821.7+612.821]"52"

DISTINCTIONS REFERABLE TO SLEEP, CIRCADIAN RHYTHM OF PHYSIOLOGICAL FUNCTIONS AND PARAMETERS OF MAN'S PERFORMANCE ON THE FIRST DAY AFTER CHANGING FROM THE USUAL SCHEDULE TO SPLIT PERIODS OF ALTERNATE SLEEP AND WAKEFULNESS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 22-25

[Article by A. N. Litsov, submitted 6 Jun 80]

[English abstract from source] The effects of sectionated and shifted work-rest cycles on diurnal variations of physiological functions, mental performance and sleep parameters have been studied. It has been demonstrated that the first day on sectionated work-rest cycles brings about the least changes. It has been concluded that the sectionated work-rest cycles can be recommended for transitional-based schedules of scientists working in an unusual environment.

[Text] One of the central problems of industrial physiology and psychology is the work and rest schedule for an operator when he spends a long time in an unusual habitat and is forced to alter the daily schedule (cosmonauts, pilots, sailors and others). Special studies have established that use of numerous (split) sleeping-waking cycles is associated with marked disturbances referable to performance and sleep in most people [1-3], as well as general decrease in reliability and efficiency of professional operator work [4-5].

At the same time, studies revealed that some of the split schedules used do not have an appreciable effect on functional state and performance of man, particularly for the first few days [3, 6-8]. Such dissimilarity of the effects of different variants of split sleeping-waking schedules on man, as well as the high likelihood of using them in a number of modern professions, makes it imperative to pursue a more comprehensive study of such schedules in the interests of optimizing man's professional performance.

Our main objective here was to make a comparative evaluation of the effects of some versions of split sleeping-waking schedules on functional state and performance of an operator, and to determine whether such schedules can be used as transitional ones (for 1-3 days) when the daily cyclogram of his work has to be changed.

Methods

We conducted these studies on 23 healthy male volunteers 25-48 years of age, who were divided into 7 groups. For the first group (3 subjects) there were 2 sleep periods, from 2300 to 0300 hours and 1400 to 1800 hours; for the second (6 people), 3 sleep periods, from 2300 to 0200, from 0500 to 0800 and from 1300 to 1600 hours; for the third (2 men), 3 periods, from 2000 to 2300, 0400 to 0700 and 1400-1700 hours; for the fourth (3 men), 3 sleep periods, from 1400 to 1700, 2000 to 2300 and 0400 to 0700 hours; for the fifth (3 people), 3 sleep periods, from 1400 to 1700, 2200 to 0100 and 0800 to 1100 hours; for the sixth(4 men), 2 sleep periods, from 1000 to 1600 and from 2300 to 0100 hours; for the seventh group (2 people), 3 sleep periods, from 0800 to 1100, 1400 to 1700 and 2200 to 0100 hours.

The study was conducted in an isolated room. The hygienic parameters of the chamber were the usual: atmospheric air pressure, 18-25°C temperature, relative humidity 45-75%, artificial illumination of 150-200 lux in the waking periods and 10-15 lux during sleep.

The main condition of the study, i.e., adherence of each participant to the specified sleeping-waking schedule, was achieved by strict adherence to the daily schedule and active intervention of the researcher if it was infracted.

In the course of the studies, we recorded and analyzed the circadian rhythm of correlation between integrated activity of fast (α and β) and slow (δ and θ) waves on the electroencephalogram (EEG), heart rate (HR), mental productivity (latency periods of simple and complex motor reactions, speed of performing arithmetic operations, accuracy of estimating 20-s time intervals), quality and duration of sleep (according to EEG data, actograms and subjective evaluation).

Results and Discussion

The results of these studies revealed that a change to a split schedule of sleeping and wakefulness elicited dissimilar changes in different directions in the dynamics of the parameters studied. Thus, according to data listed in Table 1, we see that the qualitative and quantitative characteristics of sleep in different periods were directly related to duration of prior waking period, going to sleep time, as well as number of sleep periods and their duration, in the different groups of subjects. According to Table 1, the "highest" sleep parameters during the first period after changing to a new work and rest schedule were observed in the 1st and 2d groups; during the second period this applied to the 1st-3d groups, in the third period to the 5th group and, in part, the 6th and 7th groups. The longer and better sleep periods were observed on the schedule with two 4-h periods, one of which coincided (from 2300 to 0300 hours) with the start of night time and the other (1400 to 1800) was 11 h away from the first period. "High" sleep parameters were also noted in the 2d group of subjects, but only during the first two periods (2300 to 0200 and 0500 to 0800 hours), which coincided with night time. The 3d group of subjects was characterized by poorer sleep in the first period (2000 to 2300 hours), deeper sleep in the second (0400 to 0700 hours) and intermittent, shallow sleep in the third (1400 to 1700 and 2000 to 2300 hours), with some improvement in the third (0400 to 0700 hours). In the 6th group, the sleep parameters were impaired in both periods (1000 to 1600 and 2300 to 0100 hours), but more so in the second, even though it did coincide with the start of night time. Even lower sleep parameters were demonstrated in all periods for the 7th group of subjects (schedule with maximum shift of sleeping-waking cycles).

Table 1. Results of studying sleep dynamics of subjects when changing from the usual schedule to split alternation of sleep and waking periods (mean data)

Parameter	Group						
	1	2	3	4	5	6	7
Falling asleep time, min	17 17 —	18 9 81	15 6 115	20 40 13	30 67 19	19 45 —	90 35 30
Duration of sleep, % of scheduled time	87.5 93.0 —	85.0 91.6 38.8	81.7 93.3 20.6	70.4 77.7 90.3	40.0 36.1 87.2	51.0 54.1 —	47.2 50.0 97.6
Calm 5-min periods, %	72.7 65.8 —	72.5 73.3 88.7	58.0 77.6 32.5	80.6 61.8 63.8	64.7 58.3 71.7	45.8 30.1 —	49.8 47.5 57.5
Motor activity per hour	3.5 3.6 —	3.3 3.2 4.4	5.3 2.7 6.0	5.1 4.6 4.3	5.3 5.6 3.6	6.9 9.0 —	7.1 6.3 5.1
Superficial, slow-wave EEG stages, %	43.7 43.4 —	83.0 83.6 84.3	95.8 37.5 65.0	97.2 80.5 72.2	78.0 100 52.9	69.8 86.3 —	92.5 83.4 87.5
Deep, slow-wave EEG stages, %	41.7 39.9 —	12.3 14.7 10.7	4.2 41.7 31.0	2.8 13.9 22.2	13.7 0 19.4	20.8 13.7 —	6.7 12.5 12.5
Paradoxical phase, %	14.6 16.7 —	4.7 21.7 5.0	0 20.8 4.0	0 5.6 5.6	8.3 0 22.7	9.4 0 —	0.8 4.1 0

Note: Here and in Table 2, 3 values are given for each parameter, which correspond to the first, second and third periods.

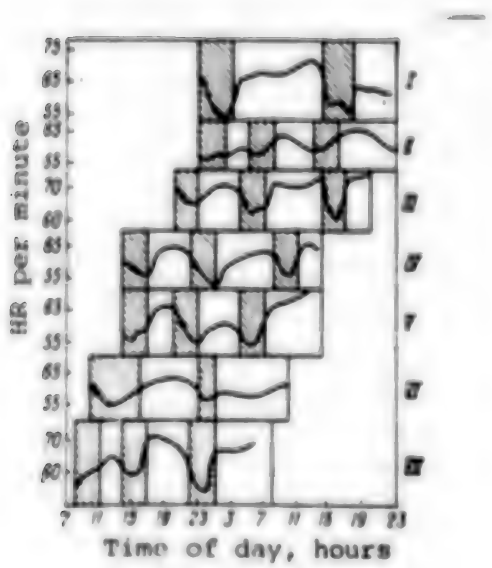

Figure 1.
Circadian dynamics of HR of subjects with different variants of split sleeping-waking schedule (mean da). Here and in Fig. 2: I-VII) 1st-7th groups, respectively

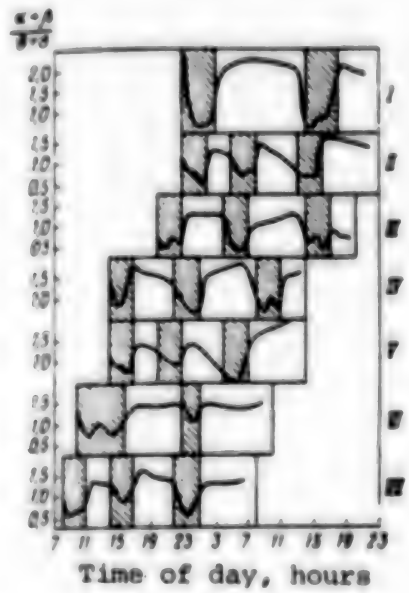

Figure 2.
Circadian dynamics of proportion of fast (α and β) and slow (θ and δ) EEG rhythms with different variants of split sleeping-waking schedules (means)

There were also distinct disturbances of parameters of circadian rhythm of the functions studied on the first day. As can be seen in Figure 1, there were two trends in the dynamics of HR with all schedules used: to assimilate the new sleeping-waking schedule and to retain fluctuations within the range of the old circadian stereotype. Thus, the 1st group of subjects showed smooth HR parameters, following the new rhythm, in the late evening and night hours. A more significant decline of HR parameters was inherent in the 2d group of subjects at night when awake, and an elevation when both awake and asleep in the daytime. The HR parameters were low in the waking period during the late evening hours in the 3d group of subjects (3-h shift of sleeping-waking cycles), whereas this applied to the night hours for the 4th and 5th groups, with a 9-h shift of cycles, with retention of unchanged parameters at other times. The 6th group (13-h shift) was characterized by a more distinct decline of HR when awake at night and in the early morning hours, while the 7th group of subjects (maximum shift of cycles) presented this in the early daytime hours also.

Table 2. Dynamics of performance parameters of subjects when changing from the usual schedule to split cycles of sleep and wakefulness (mean data)

Parameter	Group						
	1	2	3	4	5	6	7
Latency period of simple motor reaction, ms	201	279	256	262	252	231	180
	219	273	270	295	314	207	182
	—	275	239	282	304	—	175
Latency period of reaction of choice, ms	392	507	406	402	418	450	299
	413	491	476	411	438	487	332
	—	482	361	443	501	—	328
Arithmetic problem solving time, s	4.2	5.1	4.8	3.8	3.3	3.4	2.6
	4.1	4.9	4.4	4.4	3.0	4.1	2.7
	—	4.5	4.4	3.7	3.7	—	2.5
Accuracy of gauging 20-s time intervals, s	1.7	1.9	2.2	2.6	1.1	2.9	0.7
	1.8	1.4	2.3	4.8	0.8	1.1	0.7
	—	2.1	1.9	2.1	1.0	—	1.5

Similar, but less marked changes were noted in circadian dynamics of bioelectrical activity of the cerebral cortex. As shown in Figure 2, there was prevalence of α- and β-rhythms in the EEG spectrum when awake both at night and in the daytime, and slow potentials (θ and δ) during sleep. At the same time, the ratio between fast (α and β) and slow (θ and δ) EEG rhythms was higher when awake or asleep in the daytime than at night, coinciding with the HR changes, which was indicative of a lower functional state of the cerebral cortex at night and a higher one in the daytime, even when asleep [8-13].

The changes in parameters of mental productivity were also distinctly in different directions and dissimilar. As shown in Table 2, as a result of good sleep during both periods, there were virtually no changes in mental productivity of subjects in the 1st group for most tests (sensorimotor reactions, test problems, time test). Relatively minor deviations were noted (longer latency periods of motor reactions) in the 2d group (two periods of sleep at night). Analogous, but more marked

changes were noted in the 3d group of subjects who were on a schedule with a 3-h shift of sleeping-waking cycles. Significant deviations in the dynamics of mental productivity, particularly in the late evening hours (longer latency periods and desynchronization thereof) were demonstrable in the 4th group of subjects, with 9-h shift of sleeping-waking cycles. The 5th group of subjects, for whom there was the same shift but different distribution of intervals, presented some smoothing of parameters in the daytime and deterioration in the early morning and night hours. The changes were minimal in the 6th and 7th groups (some extension of latency period and increased scatter), and they were referable only to night hours, which indicates that these groups retained a higher functional state and efficiency [4, 8, 12].

Thus, the obtained data indicate that the use of a split waking-sleeping schedule causes primarily sleep disorders on the first day (up to 50-80%) and has less effect on changes in other parameters (mental productivity, circadian rhythm of functions). We demonstrated a distinct correlation between the nature of the changes that occurred and structure of the schedule (extent of shift and number of cycles). As shown by the results of our study, with the schedules with predominant splitting of sleep and waking hours, the disturbances referable to the parameters tested were minimal (1st and 2d groups), and this is apparently attributable only to the effect of intermittent sleep at night and the need to remain awake for a short period [8, 14, 15]. These deviations were more marked on schedules where the sleep-waking cycles were shifted, and with increase in the extent of the shift they gradually increased (3d-5th groups of subjects) and then decreased (6th and 7th groups). It was established that fewer sleep disorders and, consequently, less marked deviations of other parameters were observed on schedules that made maximum use of night periods for sleep (1st and 2d groups of subjects) with increase in duration of sleep to 4-6 h (1st and 6th groups), as well as with optimum distribution of duration of waking period between sleep periods (shorter at night and longer in the daytime).

To sum up the foregoing, it can be concluded that the use of split sleeping-waking schedules, though it is associated with distinct impairment of the initial state [3, 7, 8, 14, 15], causes disturbances on the first day that were not of an extent or nature to have an adverse effect on reliability and efficiency of performance. Apparently, this is the initial advantage of split waking-sleeping periods prior to a shifted work schedule, and evidently this makes them preferable for brief changes (not more than 1-2 days) in sleeping-waking schedules for specialists who work under unique living conditions. It must be assumed that one can assure maintenance of the required level of professional efficiency when there is a transient or immediate change in schedule, followed by return to the previous schedule for the day, by means of the optimum combination of waking and sleeping periods over the 24-h period.

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EMOTIONAL REACTIONS OF OPERATORS AND SLOW WAVES OF CARDIAC RHYTHM

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 26-28

[Article by A. N. Karpov and L. A. Zinov'yeva, submitted 16 Jun 80]

[English abstract from source] Simulation studies of various emotional reactions of operators have shown that sthenic emotional reactions induce inhibition of slow waves of cardiac rhythm (f = 0.05÷0.17 Hz), whereas asthenic emotional reactions lead to excitation of slow waves in the above frequency range.

[Text] Objective evaluation of emotional states in operators is still a pressing problem of aviation medicine, industrial physiology and hygiene, due to the recent increase in role of the human factor in the function of man-machine systems. A set of autonomic parameters, among which the heart rate (HR) is in first place, is generally used in aviation medicine for objective evaluation of emotional states.

With the development of electronic computer technology, autocorrelation and spectral methods gained popularity for analysis of cardiac rhythm, since they make it possible to utilize physiological information contained in a succession of cardiac cycles. Studies of recent years established the nature of changes in slow waves in the presence of some functional states [1-5]; however, we still have only a few reports concerning changes in cardiac rhythm waves in the presence of emotional stress [7, 8].

Our objective here was to study the changes in slow waves of cardiac rhythm associated with exposure of operators to different emotiogenic stimuli and to determine whether these reactions could be used as objective indicators of the emotional state.

Methods

A total of 33 essentially healthy volunteers, 24 to 46 years of age, participated in the study.

The method consisted essentially of presenting two series of slides to the subjects; the first consisting only of slides with neutral contents and the second either also neutral slides (for subjects in the first, control group) or slides, the nature of which was assumed to elicit sthenic (2d group) or asthenic (3d group) emotions.

Changes in operators' physiological parameters under the influence of emotiogenic stimuli (M±m)

Group	n	GSR (number of waves) series I	GSR series II	P	SW-1 (amplitude in relative units) series I	SW-1 series II	P	SW-2 (amplitude in relative units) series I	SW-2 series II	P	HR per minute series I	HR series II	P
First:													
subgroup A	7	4.4±1.12	2.4±1.17	0.064	0.2±0.08	0.29±0.09	0.310	0.51±0.06	0.46±0.08	0.228	76.1±4.7	76.6±4.1	0.580
subgroup B	4	5.3±0.65	3.8±0.75	0.171	0	0	—	0.72±0.04	0.73±0.04	0.443	77.8±11.2	77.6±11.9	0.567
Second:													
subgroup A	5	1.2±0.60	3.4±0.70	0.048	0.34±0.05	0.12±0.07	0.048	0.29±0.04	0.59±0.07	0.111	69.1±3.4	72.4±4.7	0.210
subgroup B	6	2.2±1.00	5.2±1.60	0.021	0	0	—	0.77±0.07	0.74±0.07	0.294	78.5±4.0	79.3±4.8	0.581
Third:													
subgroup A	5	1.6±0.70	2.8±0.61	0.111	0.17±0.10	0.47±0.04	0.048	0.56±0.10	0.34±0.04	0.155	69.6±2.6	69.1±2.0	0.565
subgroup B	6	2.2±0.74	4.8±1.07	0.032	0	0	—	0.62±0.06	0.65±0.06	0.531	74.9±4.4	74.0±4.9	0.439

Both series of slides were presented without interruptions at the rate of 12 frames/min using the Proton automatic slide projector outside the shielded, dark and relatively sound-proof chamber. With the subject seated in front of a screen in the chamber, we recorded the EKG in the D-S lead and galvanic skin reflex (GSR) by the method of Tarkhanov, using electrodes placed on the plantar and dorsal surfaces of the foot. The tracing was recorded in the paper tape of an electroencephalograph, and the EKG was also recorded on a magnetic tape recorder through the amplifier of the electroencephalograph.

The segments of tracing of the cardiac intervals, each lasting 80 s, obtained on tape were analyzed on a computer by the methods of autocorrelation and spectral analysis. The results of analysis were rendered in the form of spectral density graphs.

Results and Discussion

The Figure illustrates the spectral density plot and is a reflection of the distribution of amplitude of frequency components in a series of cardiac intervals.

Elevation of the curve in a specific frequency range is indicative of the intensity of the periodic components in a given period in the analyzed dynamic series of cardiac intervals.

Visual evaluation of changes in periodic components of cardiac rhythm is quite difficult to do directly on the graphs of spectral density, when there is a significant quanity thereof, and for this reason we have submitted here the results of our study in the form of a recap table, where the amplitudes of first-order slow waves (SW-1) and second-order slow waves (SW-2) are given in relative units, as well as the number of fast GSR waves in the series and mean HR.

We used the U criterion of Mann-Whitney to perform the procedure of checking the statistical significance of differences between the first and second series of studies. Since spectral analysis of a dynamic series lasting 60 s enables us to reliably demonstrate only SW-1, the frequency range of which is 0.05-0.17 Hz according to our observations, our reference to SW-2 is arbitrary.

For the sake of convenience of analysis, each group of subjects was divided into two subgroups. Subgroup A consisted of individuals in whose spectrum of cardiac rhythm SW-1 was present and subgroup B of operators characterized by absence of SW-1.

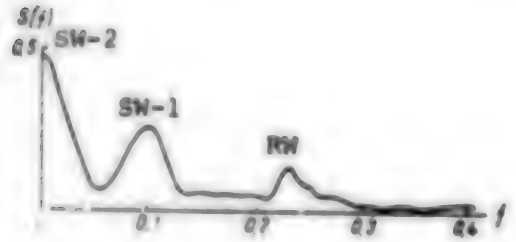
As we have already mentioned, we tried to elicit emotional reactions of the sthenic and asthenic types since, as we are profoundly convinced, a physiologist using autonomic parameters can evaluate the entire diversity of emotional reactions according to their similarity to either defense reactions (sthenic reactions) or "imaginary death" reactions (asthenic emotional reactions) [8].

In analyzing the data listed in the Table, we should first determine whether any changes in emotional state occurred in the 2d and 3d groups of subjects in the course of the study.

While there was a decrease in number of GSR waves in the control group of the second series, which can be attributed to the natural decline of emotional tension toward the end of the session, there was significant increase in number of GSR waves in both experimental groups upon presentation of the second series of slides.

These facts are indicative of emotional reactions in the experimental groups of subjects.

What influence do these reactions have on the periodic components of cardiac rhythm?



Spectrum of dynamic series of R-R intervals.
RW) respiratory waves
S(f) spectral density as a function of frequency (f)

Sthenic emotional reactions (2d group) were associated with drastic decrease in SW-1 ($P = 0.048$), whereas in the 3d group the asthenic emotional reactions led to an equally significant increase in SW-1 ($P = 0.048$). In all cases of change in SW-1 there was a change in the opposite direction in SW-2; however, these changes were unreliable (perhaps due to the greater variability of amplitude of SW-2).

It may be assumed that the changes in SW-1 are based on interaction between corticohypothalamic response reactions (response patterns) with reflexes of the homeostatic mechanism [9, 10]. In such a case, activation of the defense part of the hypothalamus (sthenic emotional reaction) should lead to suppression of these reflexes and decrease or disappearance of SW-1, which was demonstrated in our study.

As shown by the results of the studies, the changes in slow waves of cardiac rhythm have a definite and opposite direction during development of sthenic and asthenic emotional reactions. The GSR, which is a sensitive indicator of emotional reactions, did not enable us to differentiate between the reaction types, although it did clearly determine their development. The HR was found to be the least informative indicator of both degree and nature of emotional reactions.

All this warrants the belief that the changes in slow waves of cardiac rhythm will find application as objective indicators of different types of emotional reactions.

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DYNAMIC STRUCTURE OF CARDIAC RHYTHM DURING ADAPTATION TO ALTITUDE HYPOXIA

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 28-31

[Article by F. A. Shukurov and I. G. Nidekker, submitted 24 Aug 79]

[English abstract from source] On the basis of dynamic series of RR intervals of electrocardiograms of healthy male test subjects exposed for a different period of time to high altitude hypoxia, autoregression clouds were built. The patterns of distribution thus obtained were compared with physical work capacity of the test subjects. It is suggested that when selecting people to work actively at high altitudes autoregression clouds can be used as quantitative estimates of their health state and as predictions of potential adaptation failures.

[Text] There are many works dealing with evaluation of degree of adaptation of the body to high altitudes [1-7].

Our objective was to make a quantitative evaluation of adaptive and reserve capabilities of the organism in the presence of altitude hypoxia, on the basis of mathematical analysis of dynamic series of RR intervals on the EKG.

Methods

We examined 112 healthy men with similar anthropometric parameters 18 to 28 years of age. The studies were pursued in the course of a scientific expedition to East Pamirs, on transient and permanent residents of the village of Murgab (3600 m above sea level), as well as temporary residents in the suburbs of Murgab (4300 m and 4700 m above sea level) and lowland residents (840 m above sea level, Dushanbe). We divided all of the subjects into groups, depending on duration of exposure to altitude hypoxia: 1st group--lowland inhabitants living at 840 m above sea level; 2d--5th groups--those residing at 3600 m above sea level for 1-3, 4-6, 8-12 and 13-18 months, respectively; 6th group--natives of Murgab; 7th and 8th groups--individuals living temporarily (up to 3 months) at 4300 and 4700 m, respectively, above sea level.

The PWC test, as modified by V. L. Karpman et al. [8], was used to test the physical fitness of all subjects. To analyze the dynamics of cardiac rhythm, we took electrocardiograms (EKG) in the DS lead and according to Neb continuously at rest (2 min), during exercise corresponding to 375 and 625 kg-m/min for 5 min at each level, and in the recovery period which lasted 3 min after the first test and 11 min after the

second. Mathematical analysis of dynamic series of RR intervals yielded the digital characteristics of mean duration of cardiac cycle ($\overline{RR}$), standard deviation (σ) and spread of variations (V). The autoregression "cloud" [2, 3] was constructed automatically; it represented the visual pattern of scatter and degree of internal correlation between adjacent RR intervals.

In this report, we discuss both the statistical parameters for each group and the dynamics of each of them in the course of PWC_{170}.

Results and Discussion

Analysis of the autoregression pattern of dynamic series of RR intervals for lowland dwellers at rest and with different physical loads enabled us to distinguish between three types of "clouds" each of which reflected some degree of correlation between duration of cardiac cycles in the studied series (Figure 1). The first type of distribution of RR intervals of the EKG on a plane (R_i, R_{i+1})(see Figure 1a) has an elliptic form and is characterized by the following numerical values: mean $\overline{RR}$ = 0.79, standard deviation σ = 0.10, spread V = 0.35, coefficient of correlation r = 0.84. This type is encountered in healthy people at rest. With the second type of distribution (see Figure 1b), the elliptic shape disappears, the "cloud" is compressed, reflecting a more stable rhythm. It corresponded to the following numerical characteristics: mean $\overline{RR}$ = 0.67, standard deviation σ = 0.03, spread V = 0.15 and coefficient of correlation r = 0.42. This type of distribution of RR intervals was encountered in lowland dwellers during exercise.

Figure 1.
Types of distribution of RR intervals of the EKG on a plane (R_i OR_{i+1}).
a) first type of distribution (resting "cloud")
b) second type of distribution (load "cloud")
c) third type of distribution (adaptation "cloud")

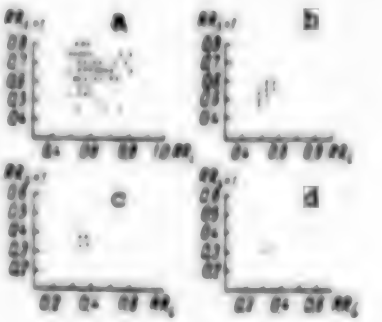

Figure 2.
Link between type of distribution of RR intervals of the EKG and physical fitness of the subjects
a-d) physical fitness corresponding to 1320, 850, 620 and 557 kg-m/min

The results of our studies and data in the literature [9, 10] enable us to show one more type of distribution of RR intervals on a plane (R_i, R_{i+1})(see Figure 1c) characterized by the following parameters: mean $\overline{RR}$ = 0.94, standard deviation σ = 0.85, spread V = 0.55 and coefficient of correlation η = 0.16. In the lowlands, such a distribution is encountered in healthy adolescents at rest.

Statistical analysis of dynamic series of RR intervals at rest yielded all three types of distribution, the incidence of which depended on duration of stay at high altitude, in permanent residents and individuals living temporarily (for 3 days to 1.5 years) at altitudes of 3600, 4300 and 4700 m above sea level (see Table).

Incidence of different types of distribution of RR intervals on the EKG of subjects in different groups

Group of subjects	Type of distribution, %		
	first	second	third
1	63.16	15.79	21.05
2	36.36	45.46	18.18
3	46.15	7.70	46.15
4	61.90	9.52	28.58
5	64.29	35.71	—
6	56.33	25.00	16.67
7	—	100.00	—
8	44.44	55.56	—

The largest number of subjects with the second type of distribution (see Figure 1b) was observed during the short stays at high altitude (up to 3 months). Evidently, the presence of this type of distribution at rest, at high altitude, is indicative of the mode of cardiac function that is inherent in the emergency phase of acclimatization [3], i.e., in the mode of mobilization of cardiac function to "fight" for oxygen. Since this type of distribution was encountered in the control group only during exercise, we named it the load "cloud." Longer stays at high altitude (4-6 months) were characterized essentially by the third type of distribution (see Figure 1c), which probably reflects the mode of cardiac function in the transitional phase of acclimatization. At this time, there is a change in regulation of cardiac rhythm to a more advantageous mode, so that we called this type of distribution the adaptation "cloud."

With further increase in duration of stay at high altitude (over 1 year), there was an increase in number of subjects with the first type of distribution (see Figure 1a), which is apparently indicative of establishment of a new, more advantageous mode of cardiac function during the phase of stable adaptation. We named this type of distribution the "resting cloud." We found the type of "cloud" illustrated on the left of Figure 1a, which differs slightly from the one on the right of Figure 1a in that the rhythm is slower and there is somewhat greater scatter, the most often among the permanent highland residents.

Figure 2 illustrates the dynamics of change in types of distribution with exercise corresponding to 625 kg-m/min in subjects differing in maximum physical work capacity. With decrease in capacity there was stabilization of rhythm, less scatter and decreased correlation between adjacent RR intervals. A comparison of the types of distribution during exercise to the maximum physical capacity (calculated from the results of the PWC_{170} test) confirmed the idea encountered in the literature [11] that one can make a quantitative evaluation (in our case, the autoregression "cloud") of the reserve capability of the heart.

A comparison of types of distribution to physical work capacity of each subject as a function of time spent in the highlands (at rest) revealed that the first stage of the stay at high altitude is characterized by the second type of distribution, but the first type is the optimum (from the standpoint of work capacity). With

increase in time spent in the highlands, retention of the second type of distribution was usually associated with decrease in work capacity of these subjects, and this can apparently be attributed to deadaptation. The change from the second type of distribution to the first in the 4th and 6th months of the stay in the highlands was inherent in individuals who were better conditioned for hypoxia. For less conditioned ones, adequate adaptation to the altitude was characterized by a change from the first type of distribution (1-3 months) to the first (6-12 months) with the third type between them (4-6 months). In our opinion, persistence of the second and third types in subjects spending more than 8-12 months in the highlands should be considered an adverse reaction to hypoxia.

Thus, quantitative analysis of dynamic series of RR intervals of the EKG at rest for individuals spending different periods of time under hypoxic conditions leads us to conclude that the first type of distribution characterizes the normal type of regulation of sinus rhythm with optimum coordination of branches of the autonomic nervous system. The second and third types of distribution reflect signs of discoordination in branches of the autonomic nervous system with prevalence of the sympathetic (second type--sympathotonic type of regulation) or parasympathetic (third type--vagotonic type of regulation) nervous system. Evidently, one can judge the reliability and adequacy of adaptation to high altitudes on the basis of change in type of distribution of RR intervals at different stages of visits in the highlands, at rest and during physical exercise.

The results we obtained warrant the assumption that the autoregression "cloud" can be used to evaluate the condition of individuals who lead an active life at high altitudes.

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MATHEMATICAL MODELING OF HUMAN CARDIOVASCULAR SYSTEM REACTIONS DURING POSTURAL AND EXERCISE TESTS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 31-34

[Article by I. V. Arsent'yeva, submitted 7 Aug 79]

[English abstract from source] The paper presents a mathematical model of the human cardiovascular system consisting of 34 compartments that represent arterial and venous subsystems of the systemic and pulmonary circulation, arterio-venous capillaries, right and left ventricles and atria of the heart. The model describes pulsating blood flows, changes in the pressures and volumes during a cardiac cycle in each compartment. The model has been used to study cardiovascular reactions to exercises and to determine efficiency of different compensatory reactions to postural tests.

[Text] In recent years, increasingly active use is being made of mathematical modeling for theoretical research on physiological mechanisms [1, 3]. However, there has not yet been sufficient theoretical and model development of such questions as the effects of gravity factors on function of the cardiovascular system [CVS], which is of direct interest to space medicine.

We submit here a mathematical model of the CVS, used to study dynamic reactions of the system to postural and exercise tests.

Methods

The object of our study was a mathematical model of the human CVS, a simplified flowchart of which is illustrated in Figure 1. We examined nonlinear functions of elasticity of vascular walls in some parts of the CVS, action of venous valves and variable vascular resistance. To describe pulsating blood flow in a resilient tube, we used the equations of Navier-Stokes in the differential form [4]. This resulted in the following systems of equations for different parts of the CVS, for compartments with nonlinear elasticity of vascular walls

$$\left.\begin{aligned} L_K \frac{dQ_K^{en}}{dt} &= P_{K-1} - P_K - R_K Q_K^{en} + G_K \\ \frac{dV_K}{dt} &= Q_K^{en} - Q_K^{ex} \\ P_K(t) &= S_K[V_K(t)] \end{aligned}\right\};$$

and for compartments with linear elasticity of vascular walls:

$$C_K \frac{dP_K}{dt} = Q_K^{en} - Q_K^{ex}.$$

where P_K is pressure in the Kth compartment, Q_K^{en} and Q_K^{ex} are blood flow at the entrance and exit of the Kth compartment, G_K is hydrostatic pressure in the Kth compartment attributable to gravity factors, V_K is blood volume in the Kth compartment, S_K is the characteristic of nonlinear pressure-volume function for the Kth compartment, L_K is the coefficient of inertia of the Kth compartment, R_K is resistance of the Kth compartment and G_K is extensibility [elasticity] of the Kth compartment.

In these equations, indexes L_K, R_K, G_K and C_K were determined on the basis of known physiological data [5], using the method in [4]. We took into consideration the extravascular pressure in the chest (intrapleural), abdominal cavity (intra-abdominal) and legs (muscle pump).

In this study, we examined a four-chamber model of the heart and valves. Pumping activity of the cardiac chambers was simulated by changing the rigidity of the chamber walls at different times:

$$P_i(t) = \varkappa_i(t) \cdot \left[V_i(t) - V_{st}^i\right].$$

where P_i is pressure in the ith chamber, V_i is the volume of the ith chamber, V_{st}^i is the stationary volume of the ith chamber, $\varkappa_i$ is the coefficient of rigidity of the walls of the ith chamber. Here:

$$\varkappa_i(t) = \begin{cases} \varkappa_i^{dias} + (\varkappa_i^{syst} - \varkappa_i^{dias}) \times \\ \times \sin\left(\frac{\pi t}{T_{syst}}\right), \quad 0 \leqslant t \leqslant T_{syst}, \\ \varkappa_i^{dias} \qquad T_{syst} < t < T_{ser.} \end{cases}$$

[heart?]

The ratios of duration of systole and diastole (T_{syst} and T_{dias}) for the atria and ventricles were determined on the basis of data in [6].

Results and Discussion

With the use of orthostatic factors, it was particularly interesting to compare the effectiveness of various compensatory reactions and consider the mechanisms involved in hemodynamic changes. In simulating the regulatory systems, it was assumed that arterial pressure level is regulated according to the principle of a proportional regular, and we took into consideration the presence of baroreceptor reflexes from the carotid sinus and aortic arch. The heart (heart rate--HR, force of cardiac contractions) and vessels (resistance, elasticity) were the controllable elements. The model enabled us to evaluate various hypothesis concerning regulation of peripheral resistance and elasticity of different parts of the vascular bed when moving from horizontal to vertical position. The orthostatic test was simulated in the model by changing G_K parameters at different times.

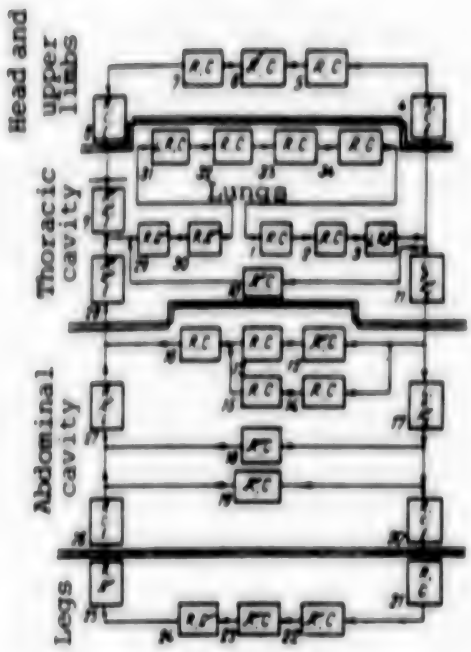

Figure 1.
Simplified flow chart of circulatory system model

1) left atrium
2) left ventricle
3) ascending aorta and aortic arch
4) common carotid arteries
5) internal carotid arteries
6) capillaries of head and upper limbs
7) small veins of head and upper limbs
8) jugular veins
9) superior vena cava
10) coronary vessels
11) thoracic aorta
12) superior mesentery arteries
13) superior mesentery veins
14) inferior mesentery arteries
15) inferior mesentery veins
16) portal veins
17) abdominal aorta
18) renal arteries and veins
19) arteries, veins of bones and marrow
20) common iliac arteries
21-) fine arteries, arterioles, capillar-
25) ies, venules and fine leg veins
26) iliac and femoral veins
27) abdominal inferior vena cava
28) thoracic inferior vena cava
29) right atrium
30) right ventricle
31) pulmonary artery
32,33) pulmonary arterioles and capillaries

Other designations explained in text.

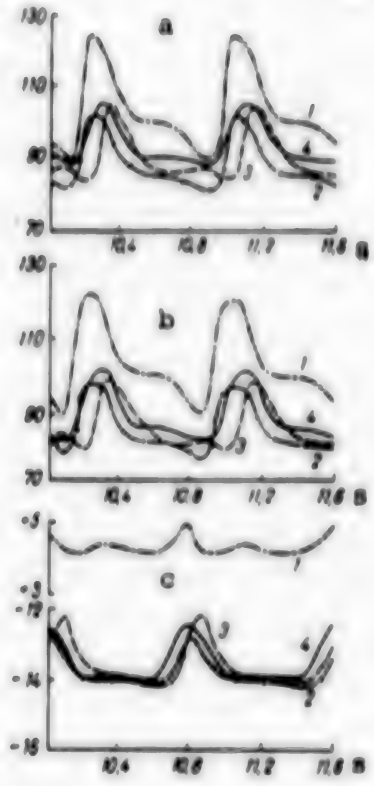

Figure 2.
Arterial and venous pressure reaction to orthostatic position

a) pressure in ascending aorta and aortic arch (mm Hg)
b) pressure in common carotid arteries
c) pressure in jugular veins (mm Hg)
1) supine state without consideration of controlling influences
2) change from supine to standing position
3) erect state with control of HR from baroreceptors
4) consideration of additional control by resistance of arterial vessels of the legs

X-axis, time after 10th s of instant change from supine to standing position.

Determination was made of the effect of time of change to vertical position on course of the transient process in the system. Analysis of the model for sensitivity to change in various parameters revealed that the elasticity features of vascular walls have the main effect on the transitory process.

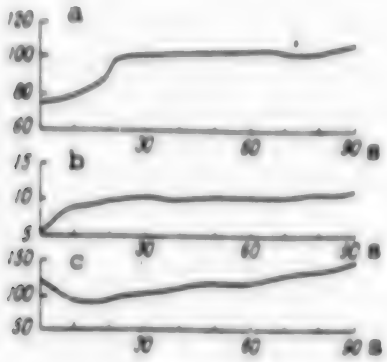

Figure 3.
Reaction of circulatory system to exercise corresponding to 600 kg-m/min in supine position. X-axis, time (seconds)

a) HR per minute
b) cardiac output (ℓ/min)
c) systolic pressure in aortic arch and ascending aorta (mm Hg)

Figure 2 illustrates some of the results of simulating behavior of the CVS during rapid change to vertical position. The results are referable to the state of the CVS after 10 s in orthostatic position. For the first 10 s after rapid change to vertical position, in the test that did not consider controlling factors, pulse pressure in the aortic arch dropped from 37 to 22 mm Hg and pulse pressure in the carotid sinus from 35 to 19 mm Hg. Minute volume decreased from 5.6 to 3.45 ℓ/min and HR remained at 75/min. The same test with control of pulse rate by baroreceptors, with maintenance of constant peripheral resistance resulted in a drop of pulse pressure in the aortic arch to 24 mm Hg and in the carotid sinus to 21 mm Hg. Minute volume constituted 3.5 ℓ/min and HR rose to 89/min. Testing with inclusion of additional control of resistance of arterial vessels of the legs led to decline of pulse pressure in the aortic arch to 24 mm Hg. Minute volume increased to 3.85 ℓ/min, with HR of 85/min. These results indicate that there was adequate change in CVS reaction to orthostatic factors when the regulatory systems were more complex.

In simulating the effect on the CVS of exercise, it was assumed that nerve signals are not extinguished during exercise, and that metabolic intensification takes place through arterial receptors [7]. In models of regulation during exercise, we examined neurogenic and metabolic factors of regulation. The components of neurogenic regulation included somatic regulation of HR and resistance in vascular system (VS) of the legs, proprioceptive regulation of resistance in VS of the legs and abdominal cavity, and baroreceptor regulation of HR. The model of metabolic factors of control describes the dynamics of oxygen uptake, oxygen debt and two integral parameters of accumulation of metabolites [8]. Metabolic regulation affects the HR, resistance of VS of the kidneys, abdominal cavity, legs, skeletal bones and coronary vessels, proportionately to the overall parameter of accumulation of metabolites and oxygen debt. Some of the results of modeling the behavior of the CVS during the exercise test on the bicycle ergometer corresponding to 600 kg-m/min in supine position are illustrated in Figure 3. The obtained results revealed that after 90 s processes were not established in the system; HR increased from 75 to 110/min. Stroke output increased slowly (from 74.6 to 105 mℓ). Thus, the increase in minute volume from 5.6 to 11.55 ℓ/min occurred mainly because of increase in HR. Mean pressure in the aortic arch rose by 14.8 mm Hg, pulse pressure rose by 23 mm Hg, mean pressure in the carotid artery by 14.5 mm Hg and pulsed pressure by 19 mm Hg. These results conform well with the experimental data. We see that the model furnishes with varying degrees of accuracy the quantitative characteristics of physiological processes in the human CVS with the factors we discussed, and it can be used as an ancillary tool in the study of the CVS for the purpose of assessing circulation in its different branches.

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MORPHOLOGICAL AND FUNCTIONAL EVALUATION OF THE EXTERNAL RESPIRATORY SYSTEM OF RABBITS WITH SUBACUTE OXYGEN TOXICITY

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 34-37

[Article by I. A. Aleksandrov, A. I. Selivra, T. Ye. Timoshenko, N. A. Ryabukha, V. A. Leosko and A. G. Bobkov, submitted 14 Jan 80]

[English abstract from source] Rabbits were exposed to hyperoxic experiments (2.5-3.0 kg/cm^2 O_2 for 3-4 h and 2.0 kg/cm^2 O_2 for 16-22 h until death) to study changes in their respiratory and cardiovascular systems. After exposure one lung was used for histological examinations under light microscope and the other to determine the surfactant stability index. It was found that serious changes in the respiratory and cardiovascular systems in all animals (including those who died during exposure) were not followed by histological changes of the lungs. Therefore, the pathogenetic mechanisms of subacute (pulmonary) oxygen intoxication are associated with disorders in the central regulation of autonomic functions rather than with direct lesions of the pulmonary tissue.

[Text] The increased use of high partial oxygen pressure in clinical practice and various areas of human endeavor makes it important to continue investigations of various problems of hyperoxia. Among them, the study of toxic effects of high oxygen pressure on the organism, the main manifestations of which amount to development of acute (convulsive), subacute (pulmonary) and general toxic form of oxygen toxicity [1], is among the important aspects. Our objective here was to make a complex study of external respiration in rabbits in the presence of oxygenation parameters that are generally used in experimental practice to simulate the pulmonary form of oxygen toxicity.

Methods

This study was conducted on 18 chinchilla rabbits (13 experimental and 5 control males) weighing 2.5-3.0 kg. All of the animals were first submitted to clinical and physiological screening. The experimental rabbits were exposed to a pressure of 2-3 kgf/cm^2 in a pressure chamber. Duration of exposure to 2.5-3.0 kgf/cm^2 oxygen pressure was 3-4 h, and exposure to 2 kgf/cm^2 lasted until the animals died. During the exposure period, we periodically recorded pneumograms on all rabbits by the method of rheoplethysmography of thoracic organs and the EKG. We estimated the respiratory rate, respiratory volume and minute volume of respiration (MV) from

the changes in respiratory waves on the pneumogram. To prevent accumulation of CO_2 in the chamber, we used a chemical absorbent and periodically aired the chamber with oxygen.

After termination of the experiment, we took tissue samples from all lobes of the left lung (2×2×2 mm) for examination of surfactant by the method of Pattle [2], from rabbits that had died or were sacrificed by administration of lysthenon (including the controls). The second lung was used for histological examination under a light microscope. The lung was fixed by injection of 10% formalin under pressure of 20 cm water column into a bronchopulmonary prepration placed in a container with formalin in the same concentration. Pieces of lung were imbedded in paraffin to prepare sections. Sections 6-7 μm in thickness were stained with hematoxylin and eosin according to Van Gieson with additional staining of elastic fibers with fuchsilin.

Results and Discussion

Our studies established that animal deaths occurred after 3-4 h of exposure to a pressure of 3 kgf/cm² (3 out of 5 rabbits died), after 4 h of exposure to 2.5 kgf/cm² (1 out of 4 died) and after 16-23 h of exposure to 2 kgf/cm² (4 out of 4 died). Thus, of the 13 experimental rabbits, 8 died. Oxygen seizures were noted in the experiments with oxygen at a pressure of 3 kgf/cm² in 3 rabbits, 2 of whom died, and at 2 kgf/cm² in 1 rabbit.

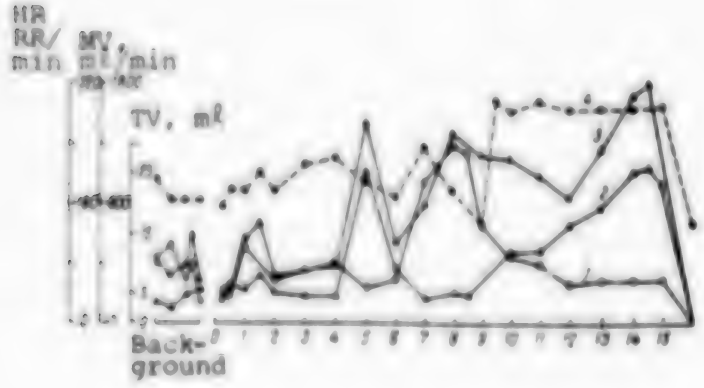

Figure 1.
Changes in respiratory rate (RR), tidal volume (TV), minute volume (MV) and heart rate (HR) of rabbit during exposure to oxygen at 2 kgf/cm² until the animal died.

1-4), RR, TV, MV and HR, respectively

During the first 1-2 h of exposure, all rabbits presented an increase in MV, chiefly due to change in respiratory volume and slowing of heart rate. Thereafter, there were periodic drastic fluctuations of MV level, which occurred in a number of cases in the presence of faster respiration with concurrent decrease in tidal volume. The heart rate increased gradually, reaching a maximum at the end of the exposure period.

Just prior to death, the animals presented sudden drastic changes in all of the parameters studied of functional state of the respiratory and cardiovascular systems (Figure 1).

Studies of pulmonary surfactant revealed that the surfactant stability index (SI) was in the range of 0.920-0.998 in all experimental animals, and it showed virtually no difference from control animals, for whom it constituted 0.912 ± 0.015. It is

believed that an SI of 0.85-1.00 or more corresponds to a normal amount of surfactant, while less than 0.71 is indicative of a distinct decline thereof [3, 4]. Thus, the results of these studies conform with the part of the rather contradictory data in the literature that is indicative of absence of distinct decline of surfactant content of the lungs under the influence of hyperoxia [5, 6].

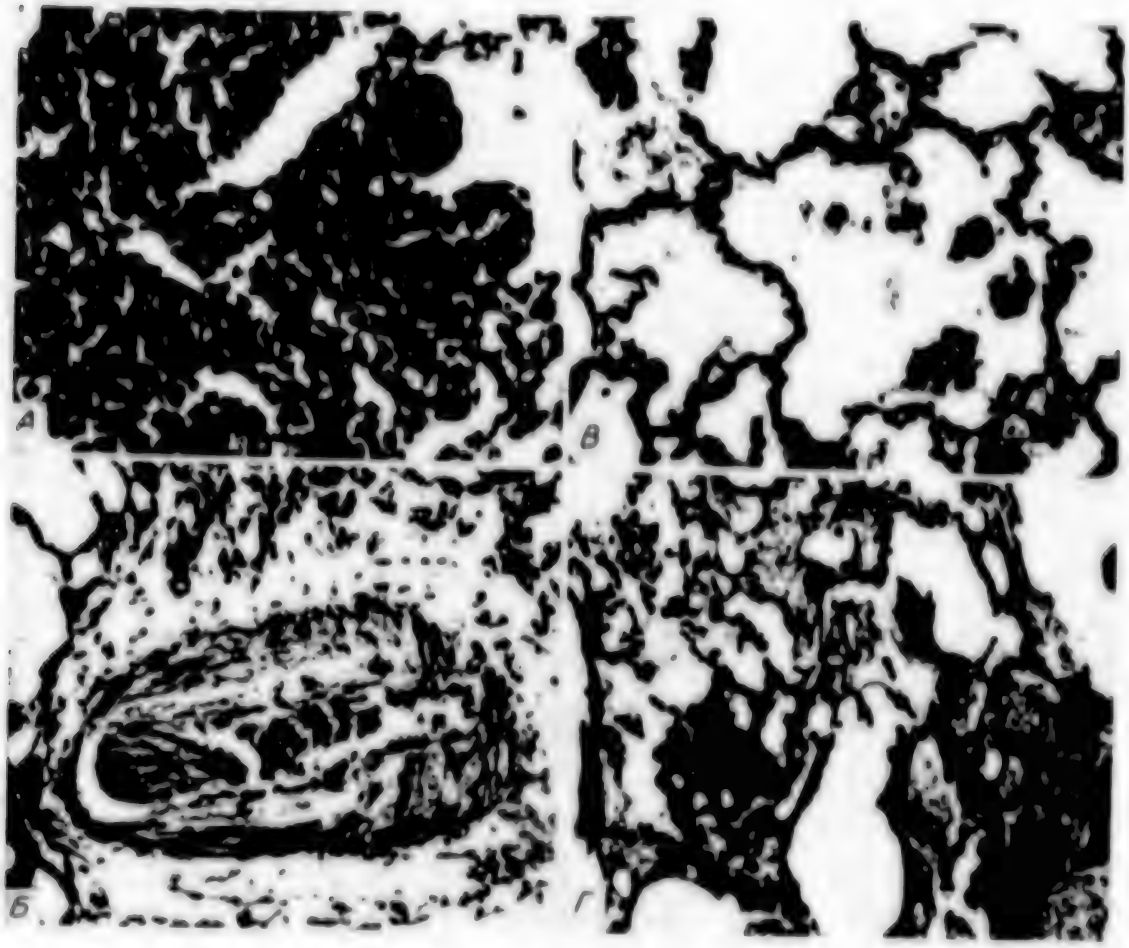

Figure 2. Microphotograph of lungs of experimental rabbits with demonstrated areas of solitary tissular changes. Hematoxylin and eosin stain; magnification 15× ocular, 20× obj.

А) area with swollen alveolar epithelium
Б) traces of edematous fluid in alveolar lumen
В) perivascular edema
Г) serous fluid with erythrocytes in alveolar lumen

The results of morphological studies revealed that in all but one experimental rabbit the lungs did not differ macroscopically from those of control animals. They were well aerated, soft, grayish-pink in color. The pleura was thin, smooth and shiny. In only 1 rabbit, exposed to oxygen at 3 kgf/cm^2 for 4 h was part of the posterior lobe of the right lung firm, with little air and dark red.

Microscopic studies revealed that there was little difference between the lungs of experimental and control animals. However, a more careful examination showed that there were scattered, solitary, fine areas of dystelectasis with plethora of capillaries of the alveolar septa, in some places with erythrocytes in the alveolar lumen. Some alveoli contained swollen desquamated cells from the alveolar epithelium (Figure 2A). More often, one could see perivascular edema, occasionally with an admixture of erythrocytes (Figure 2B). These changes were observed the most consistently in animals that died during the experiment; however, in most cases they were minimal (Figure 2B). Only when the changes in lung tissue could be seen with the naked eye was serous fluid detectable under the microscope, as well as more extensive effusion of blood into the alveolar lumen (Figure 2Г).

The morphological findings coincided with the data of other authors, who used traditional techniques for obtaining preparations and also failed to detect marked morphological changes in the canine lung under a light microscope, when dogs were exposed to oxygen at 2 kgf/cm^2 until they died, usually after 20 h [7, 8].

At the same time, Shield [8] demonstrated that, on preparations made by the method of desiccation by sublimation, one can detect overt signs of intraalveolar edema which, in the opinion of the author, developed just prior to the animals' death, within the last 3 h of exposure.

On the whole, our data corroborate the conceptions of a number of authors who stressed the leading role of the nervous system in the mechanism of development of the pulmonary form of oxygen toxicity [1, 9-11], and they conform well with the findings of Suga et al. [12], who conducted special experiments with concurrent ventilation of various lobes of the lung with hyperoxic and hypoxic gas mixtures and demonstrated greater resistance of the pulmonary parenchyma to long-term exposure to 100% oxygen at elevated pressure than the regulatory centers of the brain.

It may be assumed that the principal pathogenetic mechanisms of subacute (pulmonary) oxygen toxicity are more related to disturbances in central regulation of autonomic functions than to direct damage to lung tissue. Expressly these disturbances are the cause of death under hypoxic conditions.

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UDC: 616.748.54-091-092.9-02:[629.78+612.766.2

STRUCTURAL CHANGES IN THE SOLEUS MUSCLE OF RATS FLOWN ABOARD THE COSMOS SERIES OF BIOSATELLITES AND SUBMITTED TO HYPOKINESIA

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 37-40

[Article by Ye. I. Il'ina-Kakuyeva and V. V. Portugalov, submitted 17 Mar 80]

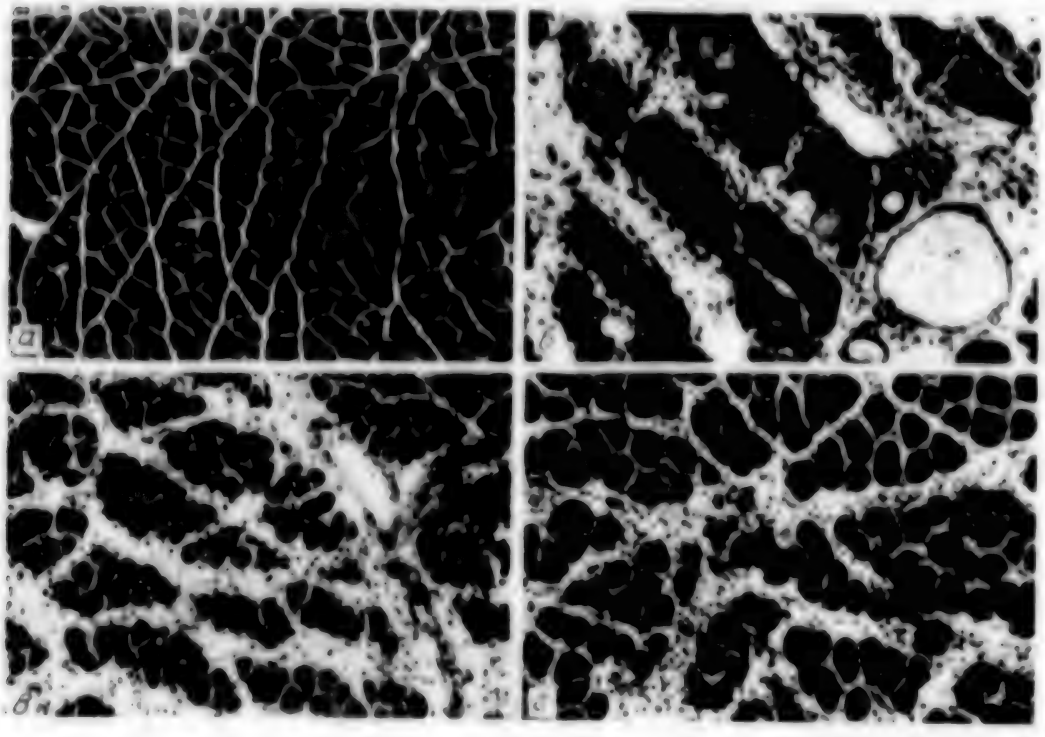
[English abstract from source] Structural changes in the soleus muscle of rats used in flight and syncrhonous experiments of the Cosmos program and hypokinetic studies have been investigated. It is hypothesized that focal edema and dystrophic changes observed in flight, synchronous and hypokinetic rats can be caused by circulation disorders of different etiology. In flight and synchronous rats they develop two days postflight due to the deconditioning of the muscle tissue and intraorgan vascular system which fail to meet the requirements after transition from 0 g to 1 g. In hypokinetic rats circulation disorders occur on the first experimental day due to mechanical causes (paws are pressed against the cage floor impeding venous outflow) and muscle pump deficiency. In all cases circulation disorders seem to be associated with peculiar features of angioarchitectonics of the soleus muscle.

[Text] It is known that weightlessness causes atrophy of skeletal muscles. Studies of skeletal muscles of rats in experiments aboard biosatellites of the Cosmos series revealed that the flight does not have the same effect on all muscles. For example, the soleus is the most affected of the antigravity muscles of the hind limbs by weightlessness. Such functional changes as slower isometric responses, loss of force and elasticity, diminished mobility and resistance to fatigue are more marked in this muscle than others [1]. It demonstrates a decrease in levels of contractile and sarcoplasmic proteins, and in their enzymatic activity [2, 3]. Functional disturbances and changes in metabolic parameters are closely linked with structural changes demonstrable by morphological tests [4-6].

On the basis of data obtained from experiments aboard four biosatellites, we have made an attempt here to explain the morphological changes in the rat soleus and to compare them to data obtained from studies of this muscle in ground-based experiments, using hypokinesia as a model of the physiological effects of weightlessness.

Results and Discussion

Much loss of soleus mass (up to 25.0-30.0%) was noted in rats following 22- and 22.5-day flights aboard Cosmos-605 and Cosmos-690 satellites, examined 2 days after landing, whereas in muscles with mixed fibers there was only moderate atrophy. The soleus presented a distinctive pathological process, manifested by development of edema associated with proliferation of connective tissue elements, against the background of signs of stasis. The endomysial layers were widened, muscle fibers, which were separated by edematous fluid, lost their polygonal shape, some of them were subject to disintegration and phagocytosis by macrophages (see Figure, *a*). The vascular lumen was dilated.



Rat's soleus: hematoxylin and eosin stain; magnification, obj. 6, 3×; oc. 6, 3×

a) 2 days after 22-day flight aboard Cosmos-605
б) 2 days after 22-day ground-based model experiment
в) hypokinesia, 3[illegible] experimental day
г) vivarium control

Later on, a repair process appeared in the areas of destruction of muscle fibers, which was associated with formation of new muscle fibers and de novo production of connective tissue, which could be seen in rat muscles on the 25th postflight day.

The atrophic process in the soleus was less marked in rats in the model (control) experiments, in which all space flight factors were simulated with the exception of weightlessness, examined 2 days after termination of the experiment, than in the flight group of rats. However, they also presented analogous changes, but they were encountered considerably less often. They could be rated as significant in only one animal (see Figure, *б*)..

The hypothesis was previously expounded [4] that this process occurs in the soleus at the end of the experiment (20th-22d day) and is the result of the effects of hypokinesia. This conclusion appeared to be valid, since similar changes were observed in the soleus in ground-based experiments on immobilized animals kept in small individual cages (see Figure, *в*) [7]. Unlike the flight group, the animals in the ground-based experiments developed edema and dystrophic changes in the muscle already on the 1st-3d day, when atrophy had not yet had time to develop. In this case, proliferation of connective tissue and edema were the first signs of a process, which led to formation of "target fibers" in the stricken muscle tissue as the experiment continued, and later to "target-like" muscle fibers. The earlier development of dystrophic processes in the muscles of animals in the ground-based experiments, as compared to the flight group, can be related to the more rigid immobilization of the rats in hypokinetic cages.

None of the rats presented the above-described changes in the soleus after 18- and 18.5-day flights (Cosmos-782 and Cosmos-936 biosatellites) or at these times in the ground-based experiments. However, the atrophic process was present in the muscle and it was more marked in the flight group of animals. The animals flown aboard Cosmos-782 and Cosmos-936 were not examined 2 days after landing, as was the case for those flown aboard Cosmos-605 and Cosmos-690, but 4.5-6 h after landing and completion of the model experiment. Examination of the rats after 25 days revealed small sites of repair tissue in the muscle, indicative of a dystrophic process, the first signs of which apparently appeared later than the postflight time at which the animals were examined. This led us to conclude that edema and subsequent changes in the soleus do not occur while the animals are in flight or the model experiment, but 2 days after the experiments [8].

It was previously assumed that the disturbances observed in the soleus of animals submitted to rigid hypokinesia and rats exposed to mild hypokinesia (model experiment) and weightlessness are based on hemodynamic disorders, which develop selectively in this muscle by virtue of its distinctive circulation [5]. According to anatomical data, the soleus differs from other muscles of the hind limbs in that it has unique angioarchitectonics, a greater supply of blood and considerably more blood is deposited in it than in muscles with mixed fibers [9, 10]. In the case of rigid hypokinesia, a hemodynamic disorder may develop due to mechanical compression of vessels of the hind limbs when the animal is pressed rather tightly to the floor of the hypokinetic cage, for which reason it is difficult for venous blood to flow from the legs and signs of stasis develop in this profusely vascularized muscle, leading to edema on the 1st-3d day of the experiment. Inadequate function of the "muscle pump" in a muscle that does not function satisfactorily under hypokinetic conditions may also be the cause of this edema. Perhaps both factors play a part.

In animals submitted to weightlessness and in the ground-based experiments, the hemodynamic disorders leading to edema of the muscle apparently occurred due to deconditioning of the muscular and vascular systems, the tonus of which diminishes significantly. In weightlessness, when there is no static load on the muscles, deconditioning (and, as a result, atrophy) is more marked than in animals used in

the ground-based experiments. For this reason, when the rats resumed active movement after the flight under conditions of earth's gravity, when influx of blood to the muscle increased, the venous system was unable to cope with the load put to it, and stasis of blood followed by edema developed faster in them than in animals in the model experiment, and their vascular disorders were more severe.

Atrophy, which occurred in the soleus of rats flown aboard the biosatellites, is an important, but apparently not the decisive factor in development of hemodynamic disorders, since edema developed both in atrophic muscle after the flight and in rats used in the model experiment, in whom there were minimal signs of atrophy of the muscle. Equally important is the condition of the vascular bed, which is significantly affected when the functional state of muscles changes [11]. The condition of the vascular bed is one of the prime factors in onset of a pathological process in the soleus, as confirmed by data obtained from the experiment conducted aboard the Cosmos-690 satellite and corresponding model experiment, in which rats were exposed to total-body radiation [5]. Radiation, which impairs the capillary wall [12], was an aggravating factor, in addition to weightlessness and hypokinesia, and led to considerably deeper and more extensive disorders in the soleus than in rats who were not irradiated during the flight. In the model experiment, severe signs were observed in only one rat exposed to 1060 rad, rather than 800 rad like the others, i.e., a dosage that could elicit the greatest changes in the vascular wall. In this case, edema developed against the background of mild atrophy.

Thus, comparative analysis of data obtained from studies of the soleus of rats who were in weightlessness for 18 to 22.5 days and animals kept under conditions of relatively rigid hypokinesia revealed that the dystrophic process, which developed in this muscle in both groups, is based on the same etiological factor--hemodynamic disturbance. However, the causes of circulatory disorders are not the same in each of these cases.

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ULTRASTRUCTURE OF THE RAT'S SMALL INTESTINAL MUCOSA AFTER FLIGHT ABOARD THE COSMOS-936 BIOSATELLITE

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 40-45

[Article by N. D. Yakovleva, N. A. Pogudina and R. A. Brodskiy, submitted 20 Jul 79]

[English abstract from source] The mucous membrane of the small intestine midportion of rats from the flight (weightless and centrifuged), synchronous and vivarium groups was examined electron microscopically. Ultrastructural changes were seen in all experimental groups, although their level and rate of recovery were different. Artifical gravity on Cosmos-936 did not influence those changes significantly. The data obtained suggest that the above changes are morphological manifestations of the reaction of rat small intestine to the combined effects of space flight factors.

[Text] Because of the increasing duration of space flights it is necessary to make a thorough investigation of the effects of some of the extreme factors they involve on vital systems of the organism. The digestive system is one of the human and animal systems that react to these factors in the form of significant and persistent changes, particularly the small intestine. Light optic examination of material obtained from animals flown on biosatellites failed to demonstrate appreciable structural disturbances of the small intestine attributable to weightlessness and other space flight factors [1, 2]. The changes that were found were consistent with hemodynamic disturbances and progressive tissular hypoxia [3-6]. However, electron microscopy of the wall of the small intestine of rats submitted to a long-term space flight aboard the Cosmos-782 biosatellite revealed substantial changes in many structures of its membranes [7]. In view of the fact that the experimental conditions were the same aboard Cosmos-782 and Cosmos-936, it could be assumed that the previously described changes in the small intestinal wall should occur. Of special interest were animals submitted to artificial gravity aboard this satellite, since this made it possible to differentiate, to some extent, between morphological changes inherent in the effects of weightlessness, which could not be done in the preceding experiment.

Methods

Segments of the central part of the small intestine of rats in the flight group, in a synchronous ground-based experiment (with and without the use of a centrifuge) and vivarium control rats were submitted to electron microscopy. The material

for examination was taken a few hours after the biosatellite landed and after 25 days of the period of readaptation to earth's conditions; it was fixed in paraformaldehyde with additional fixing with 1% OsO_4; ultrafine sections were cut on an LKB-2 ultratome and contrasted by the modified Reynolds method, and they were examined under JEM-5y and JEM-100s electron microscopes.

Figure 1. Enterocytes of small intestine of flight group of rats after landing. Microvilli are destroyed and there is an accumulation of lipid droplets. Magnification 10,500×

MB) microvilli LK) lipid droplets

Figure 2. Enterocytes at the base of villi of flight group of rats after landing. Fragmentation of basal segments of enterocyte cytoplasm; magnification 9250×

Э) enterocytes
Ф) cytoplasm fragments
ЛФ) partially lyzed fragments
ЭО) eosinophil
Л) lymphocyte

Results and Discussion

The data obtained from electron microscopy of the middle segment of the small intestine of rats in all experimental groups indicated that the base enterocytes of villi and particularly the cryptal region were notable for many mitochondria, ribosomes and complexes thereof--polysomes, as well as consolidation of hyaloplasm,

which was more marked in the enterocytes of the cryptae and elevations of the mucosa. The nuclei of the cryptal epithelial cells were convoluted; there was condensation of heterochromatin in karyoplasm, and it was in direct contact with the enlarged nucleoli.

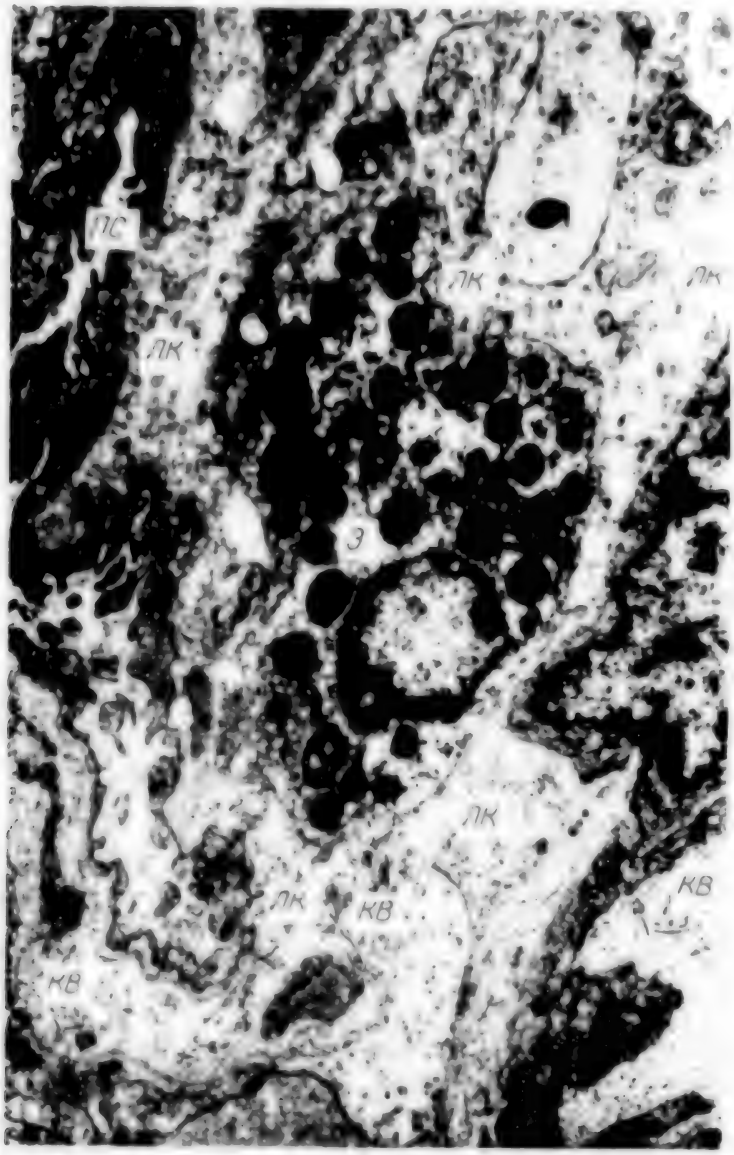

Figure 3. Stroma of central third of small intestinal villus of rat from flight group after landing. Magnification 6600×

Г) mast cell
ПС) vascular lumen
КВ) collagen fibers
ЛК) lipid droplets

Destruction of microvilli was very typical in animals of all experimental groups. Some areas thereof were swollen, became rounded and separated in the form of vesicles of different size and density, so that isolated enterocytes or a group of cells next to one another were wanting in microvilli. Such enterocytes contained a large amount of polymorphic vesicles, large dark mitochondria with lyzed cristae, more marked dilatation of the endoplasmic reticulum and accumulation of a significant quantity of lipid droplets (Figure 1). Of interest is the fact that the remnants of cells with destroyed microvilli appeared to be situated on the epithelial surface, and on numerous sections we could not trace their connection with the basement membrane. The impression was created that this enterocytes were "ejected" from the epithelium, not only at the apex of the villi as normally occurs, but on its lateral surface.

Most enterocytes of elevations of the mucosa and lower third of the villi also presented a phenomenon not previously known--fragmentation of basal sections, which consisted of separation of segments containing charge-dense material of the ribosome type (Figure 2). Some of the formed fragments underwent lysis; in this case, extensive spaces were left in their place, which were optically empty or filled with structureless mass. There were many lymphocytes and eosinophils between the fragments of cytoplasm, intraepithelially. The lymphocyte cytoplasm appeared edematous and optically empty; isolated organoids were concentrated near the karyolemma.

There was less change in the mucosal stroma of the small intestine. We observed only insignificant dilatation and edema of perivascular connective tissue in the cryptal region. The capillaries contained in the basement membrane were collapsed; their endothelium was drastically thinned down, acquired high charge density and formed many microfolds, as a result of which numerous, diverse-shaped profiles of cytoplasmic processes were seen in the vascular lumen (Figure 3). A typical finding was also fenestration of the capillary wall directed toward the center of the villi. We often observed accumulation of large quantities of fine lipid droplets around the vessels, in perivascular connective tissue (see Figure 3).

After 25 days of readaptation to earth, there was a decrease in density of enterocyte hyaloplasm and lower third of the villi; the profiles of mitochondria, membranes of the endoplasmic reticulum and Golgi's complex became more distinct.

As at the preceding examination, all experimental groups of animals revealed circumscribed areas of "microerosion," occasionally involving solitary enterocytes or several adjacent cells. There are several successive stages of formation thereof: fragmentation of microvilli, destruction of the limiting membrane of the apical part of the cell, swelling of mitochondria, dilatation of endoplasmic reticulum and subsequent "tapering" of enterocytes.

Fragmentation of basal cytoplasmic regions of most enterocytes also persisted, and the boundaries of the fragments became more distinct (Figure 4). As in the earlier studies, we observed in this region accumulation of many lymphocytes and eosinophils. Most of the fragmented areas had been submitted to lysis by this time.

The capillaries of the basement membrane remained collapsed; numerous processes of endothelial cytoplasm directed into their lumen were consistently present. Fine droplets of lipid were demonstrable in the vascular lumen at this time, rather than perivascular connective tissue.

Figure 4. Enterocytes of lower third of small intestinal villi of rats in synchronous experiment, 25 days after "landing." Explanation given in the text. Magnification 12,500×

The fragmentation of basal sections of enterocyte cytoplasm and "tapering" of epithelial cells on the lateral surface of the villi is an interesting phenomenon, which apparently reflects a state of "edema" of enterocytes under space flight conditions.

Thus, the changes demonstrable by electron microscopy of the small intestinal wall are not specific, and they can be interpreted as a morphological expression of the reaction of the small intestine to the combined effect of space flight

factors, since they were inherent in all experimental groups of animals. It must be noted, however, that they were somewhat less marked in animals in the synchronous ground-based experiment; these animals also presented fuller recovery of ultrastructure in the readaptation period. It is also important that creation of artificial gravity in this experiment, with the use of a centrifuge, did not have an appreciable effect on the direction of changes.

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CATECHOLAMINES AND ENZYMES OF THEIR METABOLISM IN THE RAT MYOCARDIUM FOLLOWING A LONG-TERM SPACE FLIGHT

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 45-47

[Article by R. Kvetnyanski and R. A. Tigranyan, submitted 24 Dec 79]

[English abstract from source] The concentration of catecholamines and activity of enzymes involved in their synthesis and degradation, i.e., dopamine-β-hydroxylase, monoamine oxidase and catechol-O-methyl transferase, were measured in the myocardium of rats flown for 19.5 days aboard Cosmos-782 and used in the synchronous and vivarium experiments. The animals were decapitated either immediately or 26 days after completion of the experiments. The catecholamine concentration and heart mass of flight animals increased significantly whereas enzyme activity remained unchanged. It can be concluded that in space flight the concentration of catecholamines in the heart increases, exerting no effect on their synthesis or degradation.

[Text] Our objective here was to study the concentration of catecholamines (CA), as well as activity of enzymes involved in their synthesis and breakdown in the rat myocardium after a many-day space flight in order to assess the stressor effects of a long stay in space.

Methods

We conducted our studies on male Wistar-SPF (Bratislava, CSSR) rats 6-10 h and 26 days after a 19.5-day experiment aboard the Cosmos-782 biosatellite. We compared the obtained data to the results of studies conducted with intact rats and rats in a synchronous experiment, where all living and upkeep conditions of the animals in flight, with the exception of weightlessness, were simulated on the ground. Samples of isolated and purified myocardium were frozen in liquid nitrogen and stored until they were analyzed, i.e., for 6-12 days. We previously tested the effect of such storage time in a frozen state on the parameters under study and failed to demonstrate noticeable changes.

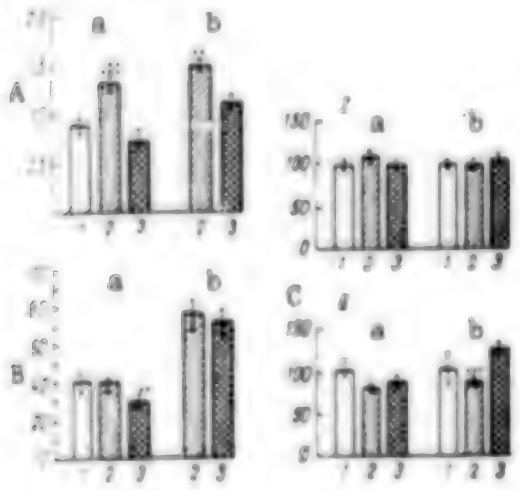
Half the myocardium was homogenized in 0.1 N $HClO_4$ so as to obtain 0.7 mg tissue in 25 µl homogenate. We took 25 µl of homogenate (0.7 mg tissue) to assay the concentration of protein [1]; the remainder of the homogenate was centrifuged under refrigeration at 10,000 r/min for 10 min. We took 25 µl of the supernatant to assay CA [2]. We determined total amounts of epinephrine and norepinephrine (NE), but since the heart contains mainly NE, the obtained data can be interpreted as the concentration of NE alone.

The second half of the myocardium was homogenized in 0.25 M saccharose so as to have 8 mg tissue per 25 µl homogenate. We took 200 µl of the homogenate, added 600 µl tris-trino X and, after 1 day, centrifuged it under refrigeration at 10,000 r/min for 10 min; we measured activity of dopamine-β-hydroxylase (DBH) [3] in 100 µl supernatant (4 mg tissue). To measure activity of monoamine oxidase (MAO), the original homogenate was diluted in 0.25 M saccharose so as to have 0.3 mg tissue per 25 µl, and we used this amount for analysis [4]. The remaining homogenate was centrifuged under refrigeration for 20 min at 10,000 r/min, and we measured activity of catechol-O-methyl transferase (COMT) [5] in 200 µl supernatant (2.4 mg tissue).

Results and Discussion

We found a reliable increase in weight of the myocardium (725±5.9 mg) in flight rats sacrificed immediately after landing, as compared to the vivarium control (623±10.8 mg) and synchronous experiment (630±12.0 mg). The mass of the myocardium of animals sacrificed 26 days after landing did not differ from that of control rats (742±7.7, 751±15.3 and 742±10.0, respectively).

There was a reliable ($P<0.01$) increase in concentration of CA in the myocardium of flight experiment rats sacrificed immediately after landing, as compared to the vivarium control and synchronous experiment (see Figure). In animals decapitated 26 days after landing, the concentration of CA in the myocardium was also reliably higher than in animals of the synchronous experiment. Unfortunately, a comparison of the obtained data to parameters for the control group could not be made for technical reasons.



CA content (A, µg/g tissue), activity of DBH (B, pmole/mg protein/h), COMT and MAO (C, I and II, respectively, % of control) in rat myocardium. In A, two dots show $P<0.02$ in relation to control group and three dots show $P<0.01$ in relation to synchronous experiment group

1) control
2) flight
3) synchronous experiment
a) immediately after flight
b) 26 days after landing

Activity of DBH (the enzyme of CA synthesis) in animals sacrificed immediately after the flight did not differ from that of rats in the vivarium control or synchronous experiment, whereas DBH activity of animals in the synchronous experiment was reliably lower than control values. Activity of myocardial DBH 26 days after the flight did not differ from the level found in animals of the synchronous experiment (see Figure).

Immediately after landing the flight group of animals presented a reliable increase in myocardial mass (by 16%, as compared to the vivarium control and synchronous experiment). In view of the fact that histological examination failed to demonstrate appreciable changes in the myocardium of these animals [6], it can be assumed that the increase in weight of the myocardium was related to an increase in number of open capillaries. It is known that the overall number of capillary cross sections per square millimeter myocardial section constitutes about 2000; only one-third of the capillaries are usually functional. Consequently, the myocardium has a large reserve of nonfunctional capillaries which could open under the influence of various factors and become filled with blood. For this reason, the mass of the myocardium could increase.

The results of our prior studies, where intensive immobilization stress was used on rats, revealed that acute stress led to a decrease in NE content of the myocardium; however, repeated stress no longer caused this parameter to decline. The stable concentration of NE in the myocardium of rats submitted to repeated stress is apparently due to increased CA synthesis, since the activity of CA-synthesizing enzymes in the heart also increased in these animals. On the basis of these data, we believed that we could have expected either a decrease in CA content of the heart of rats that had been in flight as a result of acute stress, or else a stable CA level in the myocardium as a manifestation of the nonstressor factor of space flight or adaptation of the animals to flight. However, we demonstrated a significant elevation of myocardial CA after the flight. The high CA level in the myocardium of flight rats was unrelated to a change in synthesis or breakdown of CA in the heart, as indicated by the unchanged level of DBH (CA-synthesizing enzyme), MAO and COMT (enzymes of CA degradation) activity. Increased absorption, diminished elimination of CA, altered properties of receptors, etc., could have been the causes of increased concentration of CA in the myocardium. At any rate, the elevated level of CA in the rat's heart after the space flight is indicative of a functional change in the sympathetic nervous system and, probably, the heart itself during the period of the space flight.

On the basis of our findings, it may be assumed that a long-term space flight is not an established stress-producing factor for rats.

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DEHYDROGENASE ACTIVITY IN THE PENTOSE PHOSPHATE OXIDATIVE PATHWAY AND RELATION THEREOF TO LIPID METABOLISM UNDER HYPOKINETIC CONDITIONS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 47-50

[Article by T. M. Lobova and P. P. Potapov, submitted 28 Dec 79]

[English abstract from source] The experiments were carried out on 84 white rats. At the beginning of hypokinesia activity of glucose-6-phosphate and 6-phosphogluconate dehydrogenases in the adipose tissue was decreased and in the liver, skeletal muscles and heart increased. On the 30th hypokinetic day the enzyme activity was nearly normal. The dehydrogenase activity increased by the 60th hypokinetic day in the adipose tissue and by the 90th day in the liver and heart, whereas in skeletal muscles it decreased at that experimental stage. After completion of hypokinesia the enzyme activity increased. Possible relationship between these changes in the enzyme activity and disorders of lipid metabolism during hypokinesia is discussed.

[Text] Under hypokinetic conditions there is a decrease in share of carbohydrate oxidation in supplying the organism with energy, increased mobilization of lipids from the depots and degradation thereof, as indicated by the diminished reserve of glycogen, increased lipolytic activity of adipose tissue, progressive build-up of free fatty acids (FFA) and ketone bodies in blood, and decrease in tissular triglyceride content [1, 2].

We studied here the activity of dehydrogenase reactions of the pentose phosphate pathway (PPP) of carbohydrate breakdown, which cause production of NADP·H and limit to some extent synthesis of higher fatty acids, lipogenesis and cholesterologenesis, formation of steroid hormones, nucleotides, etc., in order to determine the mechanism of metabolic disturbances under hypokinetic conditions.

Methods

Experiments were conducted on 84 male white rats weighing 180-200 g, which were kept in individual small cages made of plexiglas. The experiments lasted 7, 15, 30, 60 and 90 days. After 90 days of hypokinesia, some of the rats were transferred to ordinary cages for 15, 30 and 60 days (readaptation period). After decapitating the animals, we measured activity of glucose-6-phosphate dehydrogenase

(GPD-EC 1.1.1.49) and 6-phosphogluconate dehydrogenase (PGD--EC 1.1.1.44) in the liver, skeletal muscles, heart and adipose tissue (epididymal fat) by the method of Kornberg and Horecker as described by Yu. L. Zakhar'in [3]. Protein content was assayed by the biuret method. Enzyme activity was expressed in micromoles of substrate per gram protein per minute.

Results and Discussion

There was an increase in GPD activity in the liver, skeletal muscles and heart at the early stages of hypokinesia (Figures 1 and 2). On the 15th day it was 21.3, 45.4 and 44.5%, respectively, higher than in the control, whereas in adipose tissue it decreased by 54.2%. GPD activity of the liver remained elevated on the 30th day (by 12.9%); it did not differ appreciably from the control in the skeletal muscles and heart, and presented a tendency toward increasing (by 22.2%) in adipose tissue. On the 60th day of hypokinesia, GPD and PGD activity in the liver and heart was the same as in the control; it decreased reliably by 27.8 and 43.4%, respectively, in skeletal muscles, and increased by 41.3 and 61.6% in adipose tissue. On the 90th day, there was a tendency toward increase in GPD activity in the liver (by 11.9%) and reliable increase in PGD activity (by 17.9%). The former enzyme retained the tendency toward decline in skeletal muscles and increased by 16.2% in the heart.

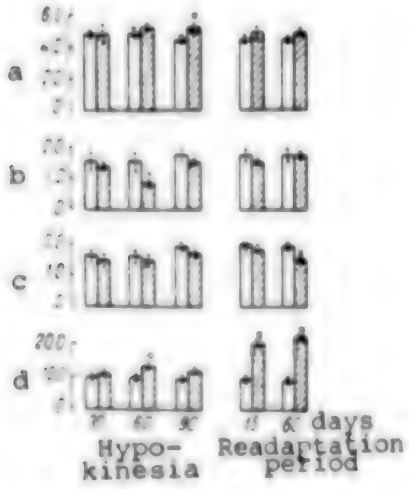

Figure 1.
GPD activity in rat tissues during hypokinesia and in readaptation period (in μM substrate/g protein/min).
Here and in Figure 2:
a) liver
b) skeletal muscle
c) heart
d) adipose tissue
White columns, control; striped, experiment. The × shows statistically reliable changes ($P<0.05$).

During the readaptation period, we observed distinct increase in activity of the tested dehydrogenases in the liver and adipose tissue at all stages, in the myocardium on the 15th and 30th days, and in skeletal muscles on the 60th day. In adipose tissue GPD activity increased by 51.8% on the 15th day, by 127.9% on the 30th and by 81.5% on the 60th day; PGD activity increased by 110.9% on the 15th day and by 148.2% on the 60th day. In liver tissue, GPD activity was reliably higher than in the control: by 9.6, 15.7 and 17.8% on the 15th, 60th and 90th days, respectively.

In analyzing the obtained data, we tried to determine whether there is a correlation between the activity of the enzymes in question and lipid metabolism, particularly since there are data in the literature indicative of a direct link between rate of lipogenesis and activity of dehydrogenases of the early stages of the PPP, which produce NADP·H [4, 5]. Depression of PPP dehydrogenases in adipose tissue on the 7th and 15th days of hypokinesia causes depression of lipid synthesis and reflects the general adaptation reaction, which is characterized by prevalence of catabolic processes. We interpret the substantial activation of PPP dehydrogenases in the liver, heart and skeletal muscles at the early stages of hypokinesia as one of the

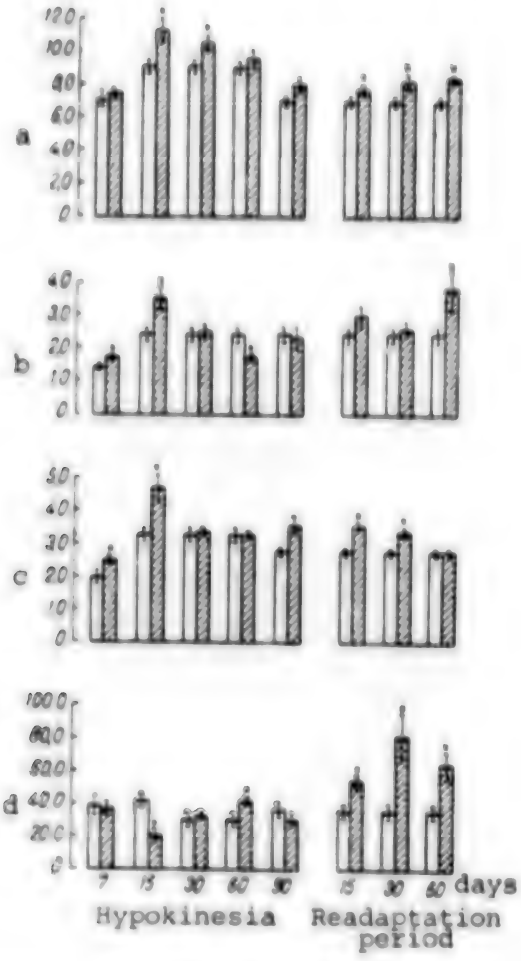

Figure 2.
PGD Activity in rat tissues during hypokinesia and readaptation period (μM substrate/g protein/min)

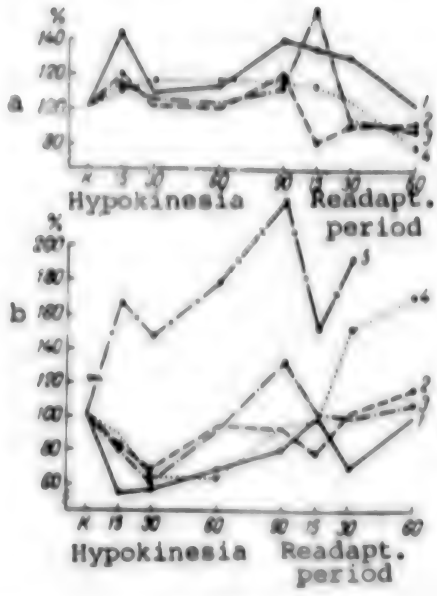

Figure 3.
Lipid content of rat blood serum and tissues during hypokinesia and in the readaptation period (% of control--K--level)
a) cholesterol
b) triglycerides, FFA
1) blood serum
2) liver
3) heart
4) skeletal muscle
5) blood serum FFA

defense and compensatory reactions to stress. However, stimulation of PPP reactions in tissues, particularly in the liver, and slowing of oxidation in the tricarboxylic acid cycle, which produces an excess of active acetate with breakdown of FFA (as indirectly indicated by ketosis), creates conditions for intensification of cholesterologenesis and leads to accumulation of cholesterol in blood and tissues (Figure 3). By the 60th day PPP activity is normalized in the liver. Interestingly enough, at this time there was a tendency toward normalization of cholesterolemia.

On the 90th day, we observed synchronized increase in activity of GPD, cholesterologenesis and lipogenesis in the myocardium, with maximum accumulation of triglycerides. In the presence of progressive ketosis of the heart, there is apparently intensification of the extramitochondrial pathway of utilizing acetoacetic acid by means of reduction thereof by NADP-dependent dehydrogenase to β-hydroxybutyrate [6], which was possibly one of the causes of increased activity of the oxidative stage of the PPP.

In our opinion, the increase in activity of PPP dehydrogenases in the liver at the late stages of hypokinesia initiated synthesis of FFA and cholesterol, and was instrumental in build-up thereof in blood (see Figure 3).

It may appear paradoxical that, with the increased activity of dehydrogenases of adipose tissue of experimental rats on the 60th day and close to normal on the 90th day of hypokinesia, there was a drastic decrease in lipid content in the depot. Evidently, hypoglycemia played an appreciable part in this effect [7]. It is known that the degree of glucose utilization by rat adipose tissue is related to its level in blood [8]. For this reason, the shortage of substrate (glucose) could have lowered the productivity of PPP dehydrogenase reactions. Moreover, in rats only glycerin synthesized de novo from glucose is used for triglyceride synthesis in adipose tissue [9]. Thus, the carbohydrate deficiency prevented fat formation in the depot.

We tend to believe that maintenance of rather high activity of PPP dehydrogenases under hypokinetic conditions, when there is prevalence of catabolic processes, is essentially adaptive in nature; it enhances the efficiency of reduction synthesis and, with the change to energy supply by fatty acids, it is instrumental in more economical use of glucose.

The build-up in PPP dehydrogenase activity in tissues after terminating hypokinetic conditions is attributable to intensification of anabolic and, in particular, protein synthesizing processes, increased nucleic acid requirements of the organism, as well as metabolites of PPP needed for their synthesis--NADP·H and pentoses. However, stimulation of dehydrogenase reactions in the PPP in adipose tissue, which enhances lipogenesis, leads to adiposity, particularly since motor activity (and consequently energy expenditure) remains lower than in the control when the animals return to ordinary living conditions [10]. On the 60th day of the readaptation period, experimental rats weighed more than controls due to accumulation of fat in the depo and tissues (particularly muscles). Thus, increased NADP·H production in tissues in the recovery period could lead to some adverse consequences, although, on the whole, activation of the PPP aids in readaptation of the organism following prolonged hypokinesia.

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USE OF SOME NUTRIENTS FROM INEDIBLE PLANT SOURCES AS FOOD

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 50-53

[Article by V. I. Fofanov, I. A. Abakumova, T. S. Gur'yeva, N. A. Tresvyatskaya, M. V. Markaryan, T. A. Smirnova and N. Ye. Panferova, submitted 20 Jul 79]

[English abstract from source] Chemical composition and biological value of nutrient substances, particularly proteins, isolated from vegetable wastes have been examined. Manned studies have demonstrated that substances obtained from higher plant wastes can be used in nutrition.

[Text] The problem of supplying the growing population with protein and energy can be partially resovled by using nutrients from inedible plant sources, particularly vegetable crop waste [1-8]. There is information in the literature indicative of the possibility of using nutrients from some higher plants previously not used as food, after appropriate technological and culinary processing [9-11].

The present work is the result of our study of possible use as food of a maximum amount of higher plant biomass raised in a "space green house" [12-17]. The chemical composition of juice obtained from the waste of higher plants is listed in Tables 1 and 2. The amounts of protein, ash and some vitamins in the listed juices are higher than in the edible part of the vegetables.

We calculated the E/T, A/E ratios (Tables 3 and 4) and chemical score--CS [18-20] to describe more fully the biological value of the protein in the products studied.

Estimation of the chemical score established that valine, lysine and isoleucine are the limiting amino acids for juice from cabbage leaves, leucine, isoleucine and valine are such amino acids for carrot top juice, and threonine for beet top juice; the CS of these amino acids is in the range of 60 to 87%.

Estimates revealed that the biological value of juice protein is lower than that of casein, and for this reason it cannot be used as the only source of protein in the diet of man and animals. However, it can be used as a source of supplemental protein, minerals and vitamins, provided it does not elicit any dyspeptic disorders or signs of poisoning.

We conducted 2 experiments on 60 male rats weighing about 195 g to investigate this aspect. Before putting the animals on the experimental diets, they were

kept off all protein for 2 weeks, as a result of which weight loss constituted 25%. The animals were kept on the experimental diets for 15 days.

Table 1. Nutrient and vitamin content in juices from vegetable crop tops (% dry mass)

Plant	Substance				
	protein	carbo-hydrates	ash	carotene	ascorbic acid
Potato	24.4 (6.6)	40.0 (75.1)	28.4 (3.6)	0.2(traces	7.0 (10.0)
Tomato	33.6 (9.2)	17.0 (66.0)	19.1 (12.0)	0.4 (2.0)	20.0 (40.0)
Carrot	20.0 (9.2)	— (58.4)	— (5.3)	8.7 (9.0)	11.5 (5.0)
Beet	21.0 (9.2)	38.0 (64.0)	22.1 (6.1)	Traces —	10.9 (18.8)
White cabbage	15.0 (15.0)	35.0 (48.1)	24.1 (8.0)	2.1 (traces	30.0 (30.0)

Note: The figures in parentheses refer to levels in juice from edible parts of the vegetables.

Table 2. Amino acid composition of juices extracted from the tops of higher plants (% dry mass)

Amino acid	Juice		
	carrot	cab-bage	beet
Lysine	0.8	0.4	1.3
Histidine	0.3	0.1	0.6
Arginine	0.7	0.5	1.7
Aspartic acid	1.0	0.3	1.8
Threonine	0.5	0.1	0.8
Serine	0.4	0.1	0.7
Glutamic acid	1.3	0.7	3.6
Proline	0.5	0.3	0.9
Alanine	0.6	0.4	1.1
Glycine	0.8	0.3	1.2
Cystine	0.6	0.6	0.6
Valine	0.4	0.4	1.3
Methionine	0.4	0.7	0.5
Isoleucine	1.4	0.3	0.5
Leucine	1.4	0.5	1.4
Tyrosine	0.4	0.4	0.4
Phenylalanine	0.6	0.1	1.1
Tryptophan	0.07	—	—

At the end of the first experiment, the experimental group of animals weighed less than the controls; these animals consumed less of their feed and retained less nitrogen. There was some decrease in total protein and albumin content of blood serum. It must be noted that animals given beet top juice as total replacement of casein had diarrhea for the first 5 days. We cannot rule out the possibility that this was related to the presence of excessive amounts of specific constituents in the juice extracted from the tops, for example, betaine and minerals. But we failed to demonstrate any other signs of intoxication.

Table 3. Ratio of total essential amino acids to total nitrogen (E/T) in the tested products and those traditionally used as food

Product	E/T index
Juice: from carrot tops	1.6
from cabbage leaves	1.4
from beet tops	2.4
Soybean flour	2.58
Casein	3.25
Peas	2.59
Fish	2.67
Goose egg	3.22

Table 4. Ratio of quantity of each amino acid to total essential amino acids in the tested products (A/E, mg/g)

Amino acid	Juice		
	from carrot tops	from cabbage leaves	from beet tops
Isoleucine	0.268	0.143	0.166
Leucine	—	0.085	0.119
Lysine	0.154	0.114	0.154
Phenylalanine + tyrosine	0.192	0.143	0.180
Cystine+methionine	0.194	0.371	0.130
Threonine	0.096	0.028	0.090
Tryptophan	0.013	—	—
Valine	0.076	0.114	0.154

In view of the fact that we had planned to use the juice from carrot and beet tops extracted by our technology as human food, we submitted it to bacteriological analysis. It was established that no pathogenic microflora was present.

We made a preliminary study of acceptability and tolerance of the extracted products on two volunteers. While pursuing their usual activities and taking three meals daily, the subjects drank 100 mℓ beet top juice (6.8 g dry mass) and 100 mℓ carrot top juice (8.1 g dry mass) daily for 15 days. The subjects presented no complaints during this period; we observed no deviations in their general condition or function of the gastrointestinal tract. On the basis of the obtained information, we deemed it possible to prolong intake of juices obtained from vegetable waste. The studies were conducted for 45 days with the participation of one subject (26 years old, weighing 74.5 kg, height 186 cm) in a sealed chamber with a functional greenhouse. Another man (24 years old, weight 80 kg, height 171 cm) participated in the last 15 days of the tests. The products under study (juice extracted from beet and carrot tops, cabbage and pea waste) were included in the diet, which was based on the diet designed for spacecraft crews. This diet contained 114 g protein, 92 g fat and 270 g carbohydrates. The caloric value of the diet constituted a mean of 2415 kcal/day; its low caloric value is attributable to the fact that the subjects were in a confined space and motor activity was limited.

The diet included items traditionally used--wheat, cabbage, carrots, peas and beets raised in the greenhouse within the sealed chamber. The juice from the waste of the vegetables was consumed after culi ary processing, and first courses were prepared with them. For the last 15 days of the study period, the set-up was more complex: we added to the subjects' diet 60 g (dry) chlorella biomass, which had been submitted to heat treatment and which was also raised in the chamber [21].

Throughout the test period the clinical and physiological parameters (temperature, pulse, respiration, EKG) were in the range of the physiological norm.

In view of the fact that unusual items were used in the diet, we devoted special attention to metabolism and certain physiological functions. Assays of excretion of total nitrogen and nitrogen-containing components in urine (urea, ammonia, nitrogen amine, creatinine, uric acid), as well as total nitrogen in feces, failed to demonstrate any deviations from background levels. There was only some decline of blood serum total protein (from 8.86 to 7.70 g%) in subject G-v by the end of the test period, on the 37th and 43d days, which was related to a decline of some globulin fractions. We failed to detect any changes in peripheral blood. There were no changes whatsoever in parameters of lipid metabolism (total lipid content, α- and β-lipoproteins in blood serum), adrenocortical function (11- and 17-hydroxycorticosteroids), vitamin C, B_1 and B_6 levels in 24-h urine of the subjects or in dynamics of body weight. All this was indicative of an adequate diet.

The observed decrease in total protein of blood serum occurred because of a decrease in β_2- and γ_1-globulins, which had absolutely no effect on immunological resistance of the subjects (cell immunity factors, which characterize specific immunological resistance, and possible sensitization to allergens referable to the main representatives of automicroflora).

The results of testing the intestinal microflora were equally interesting. It had been previously established [22] that inclusion of chlorella biomass in a diet based on lyophilized and preserved products leads to dysbacteriosis. No signs of dysbacteriosis were observed when chlorella was used with the same diet, with inclusion of vegetables and juices from vegetable waste.

Man's work capacity is one of the significant indicators of a satisfactory diet. Determination was made of physical fitness on the basis of the step test (exercise corresponding to 600 and 800 kg-m/min), RWC_{170} parameter (amount of work performed by the subject at a pulse rate of 170/min) and motor activity (number of steps per day, measured with a pedometer). These studies revealed that fitness of the subjects did not change.

On the basis of the obtained data, it can be concluded that it is possible to use nutrients recovered from higher plant waste in the human diet. This question merits attention and requires broader investigation.

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SOME BIOCHEMICAL PARAMETERS OF HEALTHY MAN IN A SEALED CHAMBER WITH PERIODIC IONIZATION OF AIR

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 54-56

[Article by B. V. Anisimov, Ye. A. Zagorskaya, I. I. Lyubarskaya and I. A. Popova, submitted 12 Apr 79]

[English abstract from source] The content of 11-hydroxycorticosteroids, triglycerides and enzyme activity in blood as well as the content of 17-ketosteroids in urine of normal men kept for 16 days in an enclosure ventilated for 24-60 hours with bipolar ionized air (averaged unpolarity factor 1.58, concentration of positive ions 26-35 thous. cm^{-3} and of negative ions 16-24 thous. cm^{-3}) were measured. On DD 7-9 concentrations of 11-HOCS, triglycerides and 17-KS increased. This can be attributed to an activation of the hypophyseal-adrenal system in response to the enclosure effect. Further rapid return of the parameters to the normal may be associated with the cumulative effect of air ionization. This ionization at the doses used did not influence activities of creatine phosphokinase, asparate aminotransferase and alpha-hydroxybutyrate dehydrogenase.

[Text] Ionized air, with prevalence of positive aeroions, is one of the factors to which man is exposed in a spacecraft cabin. There has not been sufficient investigation of the effects of this type of ionization of the atmosphere on man.

We studied here different biochemical parameters of blood and urine of healthy man while in a confined space, with periodic brief sessions of ionization of the air.

Methods

This study was conducted on 4 healthy individuals 21-30 years of age, who remained in a sealed chamber, 24 m^3 in size, for 16 days with relatively stable microclimate: temperature 20-22°C, relative humidity 40-70%, CO_2 and O_2 concentration 0.3-0.6 and 20-22%, respectively. The caloric value of their diet constituted 3000 kcal/day. Energy expended in daily exercise, which the subjects performed once a day for an hour, constituted 400 kcal.

An ARK1-2 automatic regulator of atmospheric ion concentration was used to ionize the air by means of the radioactive isotope, ^{14}C. There were six aeroion

generators in the chamber. Fans propelled air through the aeroion generators at the rate of 2.5 m^3/min. During the periods between cycles of ionization, the same ventilation conditions were maintained in the chamber as when the aeroion generators were working. The concentration of aeroions was close to that expected in actual space flight, constituting 35,200 and 26,100/cm^3 for positive ions in the middle of the chamber and in the sleeping place, 24,300 and 16,100/cm^3, respectively, for negative ions. The unipolarity index constituted a mean of 1.58. The first cycle of ionization, which lasted 24 h, was performed on the 4th-5th day spent by the subjects in the chamber; the next two cycles, each lasting 60 h, were on the 7th-9th and 11th-13th days, and the last one, which lasted 48 h, was on the 15th-16th days of the study. The parameters were examined 13 and 7 days prior to the start of the study (background), on the 2d, 7th, 9th, 13th and 16th days in the sealed chamber, and on the 2d, 7th days after the test (aftereffect period). We assayed the following in venous blood serum taken in the morning on a fasting stomach: concentration of 11-hydroxycorticosteroids (11-HC) by the fluorimetric method [1]; activity of creatine phosphokinase (CPK), aspartate aminotransferase (AAT) and β-hydroxybutyrate dehydrogenase (HBD) by spectrophotometric methods [2-3]. We assayed triglycerides in blood plasma by the spectrophotometric enzymatic method using prepared reagent kits [4]. We examined levels of 17-ketogenic steroids (KS) in 24-h urine collected on the day before taking blood by the spectrophotometric method [5]. The obtained data were submitted to statistical processing using the criteria of Student (Fisher).

Results and Discussion

The Table shows that the blood and urine parameters examined were in the normal range at all tested times; however, specific dynamics were inherent in each of the selected biochemical dynamics.

Levels of 11-HC, triglycerides, activity of enzymes in blood and concentration of KS in urine

Conditions	Time of examin.	11-HC, mg%	KS, mg/day	Triglycerides, mg%	CPK, IU/ml	AAT, IU/ml	HBD, IU/ml
Background Experiment	13	13.5±0.9	8.1±1.8	122.6±16.9	35.2±9.6	9.0±2.4	59.0±5.7
	7	12.4±1.1	9.2±2.5	117.9±10.2	36.7±5.9	7.0±2.2	69.7±4.7
	2	14.5±0.9	11.0±0.7	133.9±30.6	25.8±3.6	7.2±0.9	59.8±11.0
	7	18.8±1.8*	12.6±1.9*	148.9±10.3	24.8±3.9	8.6±1.6	71.2±4.0
	9	17.2±1.7*	11.1±1.3	123.0±19.9	20.3±7.7	8.6±1.1	68.2±4.4
	13	15.2±1.1	10.9±1.8	92.7±17.1	21.2±1.8	8.0±0.1	79.5±7.5
	16	15.5±0.5*	10.2±2.7	86.0±13.8	23.5±2.4	8.8±0.8	70.7±8.2
Aftereffect	2	14.5±1.2	7.8±1.1	83.1±7.8	32.2±9.6*	11.2±2.1	73.0±7.2
	7	13.1±1.7	8.1±1.0	88.9±8.7	49.0±17.4	9.7±1.8	82.2±4.4
Normal range		10–23	5–20	74–172	51	18	140

*Reliable changes ($P<0.05$); $n = 4$.

Thus, while the subjects were in the chamber there was gradual increase in 11-HC content of blood, which reached a maximum on the 7th-9th day. At the same time,

there was increased excretion in urine of products of conversion of corticosteroids (KS). During the second half of the test period, starting on the 7th-9th day and until the subjects went out of the chamber, as well as in the aftereffect period, 11-HC level in blood and KS level in urine gradually declined, coming close to background values. Plasma triglyceride content was above background levels already on the 2d test day. The high triglyceride level also persisted on the 7th day, but starting on the 9th day the concentration thereof gradually decreased and stayed at a low level in the aftereffect period. AAT and HBD activity in blood serum did not undergo appreciable changes, either during the test or aftereffect period. There was some decrease in SPK activity throughout the stay in the confined compartment and some increase in the aftereffect period.

Analysis of the results of this study revealed some general trends. The increased discharge of 11-HC into blood, associated with increased elimination in urine of products of their conversion, indicates that there is gradual activation of adrenocortical function of the adrenals when healthy people are confined in a restricted living space. The increase in blood triglyceride levels may be the result of increased adrenocortical activity, since we know that adipose tissue is one of the target organs of glucocorticoids [6]. Increased adrenocortical activity is probably a manifestation of the healthy body's reaction to altered motor activity. It is known that on the first day in a 200 m^3 sealed compartment, there was a decrease to one-fourth in motor activity [7]. The change in level of exercise could perhaps also explain the decrease in CPK activity, for which skeletal muscles are the principal source for access into blood. The significant increase in CPK activity in blood in the aftereffect period is apparently a compensatory reaction occurring when man changes from a regimen of restricted movement to free motor activity, and this is associated with activation of processes of macroerg production in muscle tissue.

By the 9th day of the study, when the high adrenocortical activity of the adrenals and high triglyceride level in blood began to diminish, overall duration of air ionization in the chamber already constituted 84 h. For this reason, we cannot state that there was immediate manifestation of the effect of ionization. The decrease in corticosteroid and triglyceride content of blood with continuation of sessions of air ionization could be attributable to a dual cause: adaptation to the confined space or cumulative effect of ionization. The latter appears more likely, since there are data indicating that adaptive changes occur at a later stage when people spend long periods of time in a sealed space [8].

Thus, the demonstrated changes are apparently attributable to the effects of a set of factors: influence of toxic microimpurities, restricted mobility, mental tension and, perhaps, ionization of the air.

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TOXICOLOGICAL AND HYGIENIC STUDIES OF WATER RECYCLED FROM OXIDANT-CONTAINING FLUIDS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 56-59

[Article by Z. P. Pak, Yu. S. Koloskova, Yu. Ye. Bezumova, V. P. Petina and M. M. Spiryayeva, submitted 20 Aug 79]

[English abstract from source] Toxic-hygienic examinations of water reclaimed from peroxide-containing technical fluids have shown that the water needs further purification using sorbents that contain a reducing agent. In the absence of the latter the reclaimed water exerts adverse effects on certain hematological parameters.

[Text] As shown by the flights aboard the Salyut-3, Salyut-4 and Salyut-5 orbital stations, use of the sorption method of regeneration yields high-grade potable water without any toxic properties from the condensate of atmospheric humidity of the aircraft.

Increased demands are made of technologists, with regard to reliability and universality of the purification system, by the use of moisture-containing emissions with diverse chemical composition, including oxidants and products of their destruction as products of water regeneration. Chemical compounds in the oxidant group are biologically active, even in microquantities [1-3]. It is also known that, in a number of cases, reclaimed water that conforms with the sanitary and chemical requirements of potable water may have an adverse effect on animals [4]. For this reason, the decision that reclaimed drinking water can be used should be made on the basis of the aggregate of results of sanitary and hygienic tests, including a toxicological evaluation as the final stage.

We submit here comparative data referable to sanitary-chemical and toxicological studies of samples of water recovered from recycled fluid containing peroxides.

Methods

Two samples of recycled water recovered by the sorption method from technical waste containing peroxide compounds served as the object of our studies: sample No 1, after passage through the charge [blend?] without reduction (redoxite) and sample No 2, after passage through a charge containing a reducing agent. Tap water served as a control. All of the samples contained ionic silver in a concentration of 0.1 mg/l as a preservative. The hygienic studies of the samples of

recycled water were conducted by conventional methods [5]. Total organic substances in water were assayed according to bichromate oxidizability and total dissolved carbon on a Beckman 915-A analyzer; electric conductivity of the water was determined with the use of an Impulse conductometer. Hydrogen peroxide and products of its destruction were assayed by photocolorimetry (sensitivity of 10^{-5} mg/ℓ) and the chemiluminescence method (sensitivity 10^{-6} mg/ℓ).

Toxicological tests of regenerated water were made on hydrobiological objects (aquarium fish, daphnia, frogs) and warm-blooded animals (mongrel male white rats). Preliminary evaluation of toxicity of the water in question was made by the test on the isolated frog heart and tests for survival of aquarium fish and daphnia. We determined the effects of the samples of recycled water on erythropoiesis in fish by the method of acidity erythrograms [6] in a experiment lasting up to 60 days.

Several of the conventional toxicological methods were used to assess the effect of the water samples on warm-blooded animals: clinical observation of animal development, dynamics of their body weight; morphological studies of peripheral blood; physicochemical study of peripheral blood [6-8]; biochemical study of blood (determination of free SH group levels in whole blood [9], whole blood cholinesterase activity [10], methemoglobin and hemoglobin [11]). These studies were conducted before the experiment, on the 30th and 60th day thereof; the weight coefficient of the animals viscera was determined; morphological studies were made of internal organs and tissues of animals (liver, kidneys, spleen, stomach, large and small intestine, adrenals) when the experiment was terminated.

Throughout the experimental period, all animals (experimental and control) were kept in the vivarium on the usual diet. The tested water samples were given to the animals in graduated dishes so that a record could be kept of water intake. The obtained data were submitted to statistical processing [12].

Results and Discussion

The results of the physicochemical studies revealed that both samples of recycled water that had undergone the stage of purification conformed with the requirements for regenerated potable water.(Table 1).

The experiments with hydrobiological objects and "isolated heart" of the frog revealed that water recovered from technological fluid by sorption treatment without inclusion of reducing agents in the charge, which had satisfactory physicochemical parameters and did not contain toxic impurities (determined by the analytical method) had a marked toxic effect on fish, protozoans and rapidly depressed the function of the frog's "isolated heart." Aquarium fish died by the 30 day, daphnia after 2.5-3 h, while the rate of contraction of the "isolated heart" decreased from 49.5±3.4 min in the control to 19.7±1.7 min in the experiment.

The recycled water (sample № 2) obtained by the method of sorption purification, which involved addition of reducing agent to the charge, had no marked effect on the biological objects studied.

The index of strength of influence of the factor of the tested water in a 60-day experiment on fish erythropoiesis differed insignificantly from the control (37% in the control and 42% in the experiment).

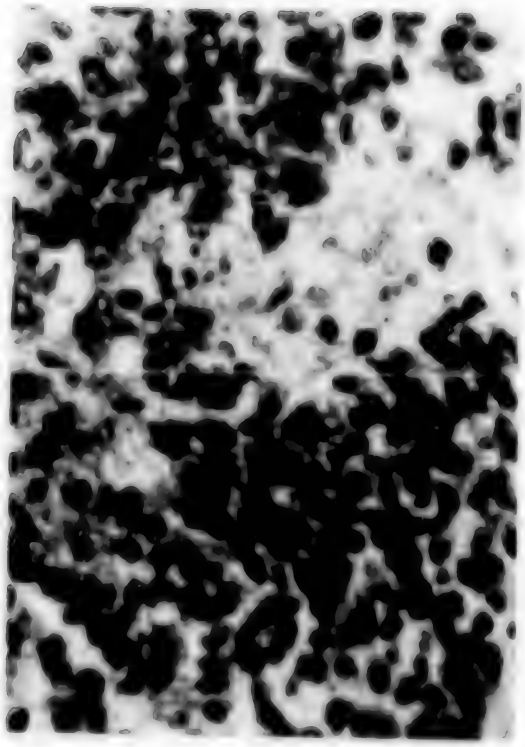

Figure 1.
Clumps of hemosiderin in cytoplasm of splenic macrophages.

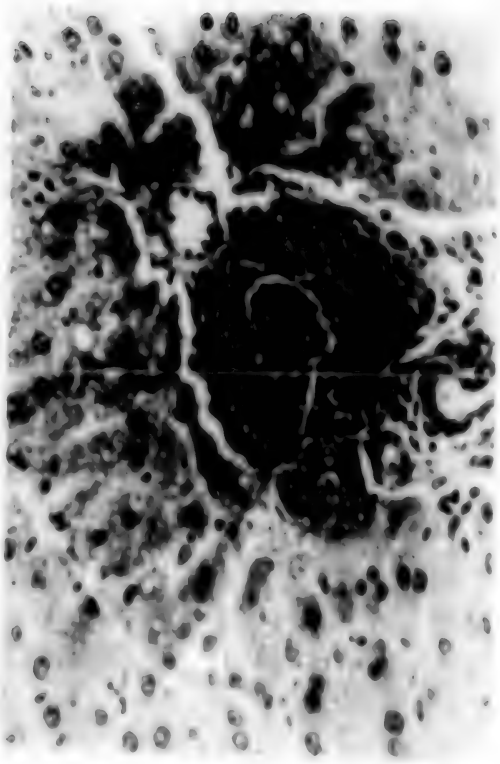

Figure 2.
Dystrophic changes in hepatocytes, with accumulation of mononuclears near vessels

In both figures: hematoxylin-eosin stain; ocular 10×, obj. 20×

Water submitted to sorption treatment on a charge without reducing agent (sample No 1) had a marked effect on warm-blooded animals. There was a statistically reliable decrease in osmotic and acidity resistance of erythrocytes, which was the most marked on the 60th experimental day. Moreover, there was a reliable increase in quantity of reticulocytes, which could be indicative of irritation of erythroid hemopoiesis (Table 2).

Studies of dynamics of methemoglobin content of blood of experimental animals revealed a reliable elevation of this parameter in the group of animals given water passed through the sorption charge without reducing agent for 60 days, as compared to both the background and experimental group of animals given water regenerated in a blend with reducing agent.

Blood cholinesterase activity decreased reliably in experimental animals on the 30th experimental day; however, it reverted to the initial level by the 60th day (see Table 2).

Table 1. Main physicochemical parameters of quality of recycled water that underwent the conditioning stage

Parameter	Sample	
	№ 1	№ 2
pH	6.1	6.0
Transparency, cm	30	30
Color, degrees	5	5
Odor, score	0	0
Flavor, score	1.0	1.0
Overall hardness, mg-eq/ℓ	3.2	2.8
Calcium, mg/ℓ	56.2	52.4
Magnesium, mg/ℓ	9.8	8.2
Sodium, mg/ℓ	41.4	36.1
Potassium, mg/ℓ	9.2	6.1
Chlorides, mg/ℓ	92.4	96.6
Nitrogen ammonia, mg/ℓ	0.1	0.1
" nitrites, mg/ℓ	0.07	0.31
" nitrates, mg/ℓ	0	0
Permanganate oxidizability, mg O_2/ℓ	0.8	0.78
Bichromate oxidizability, mg O_2/ℓ	6.0	5.4
Total carbon, mg/ℓ	5.0	5.0
Peroxide compounds, mg/ℓ	0	0
Ionic silver, mg/ℓ	0.1	0.12
Electric conductivity, C/cm	$67 \cdot 10^{-4}$	$5.1 - 10^{-4}$

Table 2. Morphological and biochemical parameters of blood of animals given the tested samples of recycled water, M±m

Parameter	Day of test	Sample		
		control	№ 1	№ 2
Leukocytes, thou/mm^3	BG	15.573±0.83	16.368±0.69	15.723±0.607
	30	15.035±1.115	17.535±1.52	18.185±1.88
	60	14.858±1.62	15.075±1.56	15.917±1.218
Erythrocytes, million/mm^3	BG	4.20±0.061	4.30±0.053	4.31±0.056
	30	4.143±0.077	4.32±0.254	4.32±0.087
	60	4.325±0.028	4.13±0.058	4.345±0.08
Reticulocytes, ‰, per 1,000 erythrocytes	BG	15.83±2.90	14.71±0.84	15.85*±1.402
	30	18.371±2.83	17.80±2.18	16.80±0.99
	60	17.330±1.24	28.28±1.26*	19.71±1.82
Hemoglobin, g%	BG	14.58±0.01	14.48±0.01	14.58±0.05
	30	14.23±0.21	13.81±0.30	14.36±0.11
	60	13.42±0.43	13.17±0.43	13.88±0.21
Methemoglobin, % Hb	BG	1.52±0.005	1.74±0.20	1.93±0.20
	30	2.44±0.441	3.59±0.26*	3.09±0.68
	60	2.58±0.004	6.70±0.91*	4.00±0.97
SH groups, mg%	BG	73.9±1.45	76.4±2.52	77.2±2.35
	30	81.6±1.76	76.5±3.00	76.2±2.69
	60	79.8±1.56	74.7±2.10	74.2±3.77
Blood cholinesterase activity, mg acetylcholine/30 min	BG	0.325±0.004	0.327±0.007	0.332±0.001
	30	0.329±0.002	0.354±0.002*	0.321±0.006
	60	0.337±0.004	0.324±0.002	0.337±0.004

*P<0.05. BG--background

Histopathological examination of the animals' viscera confirmed the results of the hematological studies: increased amount of young lymphatic and myelinic forms in the splenic pulp, follicles surrounded by a wide macrophage zone, with accumulation

of brown iron-containing pigment--hemosiderin--in the cytoplasm of many macrophages (Figure 1).

Liver tissue revealed dystrophic changes in hepatocytes and lymphoid infiltration of this organ (Figure 2). Dystrophic changes were demonstrated in the tubular epithelium of the proximal nephron segment (Figure 3). Atrophic changes were found in the gastrointestinal mucosa. No such changes were demonstrated in tissues and organs of animals given water regenerated in a sorption blend containing reducing agent.

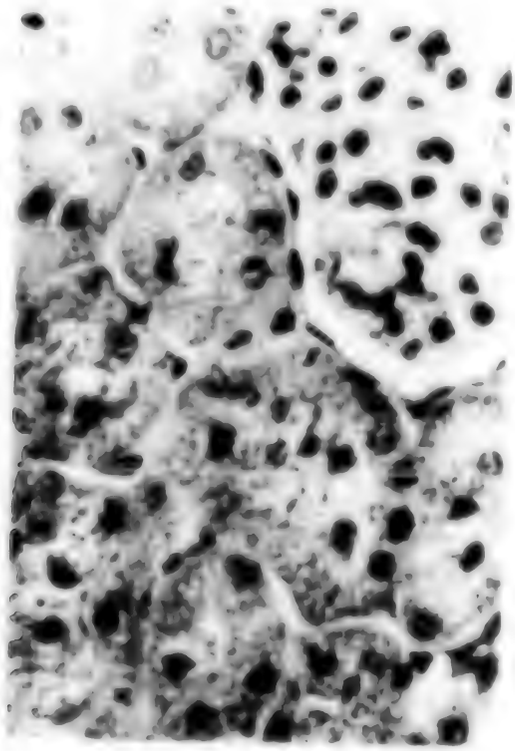

Figure 3.
Dystrophic changes in epithelium of tubules of proximal segment of nephrons. Hematoxylin-eosin stain; ocular 7×, obj. 40×

There is information in the literature to the effect that animals present changes in permeability of erythrocyte membranes, damage to mitochondrial membranes, liver and brain cells under the influence of hydroperoxides, apparently related to the effect of peroxidation of their lipids [3]. Peroxide compounds are active with regard to the enzymatic systems of erythrocytes, even in concentrations measurable in hundredths of a micromole, whereas in millimolar concentrations they distort the morphology of blood platelets [13, 14].

The results of these sanitary and toxicological studies warrant the conclusion that water recovered from the initial recycling products containing peroxide compounds requires additional sorption purification in a charge with reducing agents, since the technological system that does not contain a reducing agent does not trap products of peroxide destruction and does not assure adequate reliability of purification.

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RECOVERY OF SYNTHETIC ORGANIC ACIDS FROM HUMAN WASTE IN CLOSED LIFE SUPPORT SYSTEMS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 60-62

[Article by Yu. Ye. Sinyak and I. L. Shul'gina, submitted 20 Dec 78]

[English abstract from source] Organic acids have been obtained in an alkaline medium from a mixture of monosaccharides-carbohydrates to be used in a closed life support system. Methods of analysis of mixtures of synthetic acids have been developed. The composition of mixtures of organic acids has been identified by paper chromatography. During electrodialysis the mixtures release calcium ions. The use of mixtures of synthetic organic acids as carbon source gives rise to an intensive growth of the yeast Candida tropicalis SK-4.

[Text] One of the most difficult problems is to develop systems for producing foodstuffs aboard spacecraft and orbital stations during long-term flights. Physicochemical methods of converting human waste into substances assimilated by the body may be one of the promising means of solving this problem. Physicochemical processes for recovery of foodstuffs may also be used on earth, provided problems referable to recovery of nutrients from inedible sources are resolved.

Development of a system for producing synthetic carbohydrates occupies a special place, since they usually constitute 50% or more of man's food requirements referable to sources of energy.

We know of several schemes, according to which monosaccharide carbohydrates can be recovered from human and animal waste. As an example, we could mention the scheme of: human and animal waste → carbon dioxide → methane → formaldehyde → synthetic carbohydrates [1, 2]. With this scheme, optically inactive synthetic carbohydrates are obtained which are assimilated to a limited extent by biological objects. For this reason, it became necessary to search for other means of utilizing synthetic carbohydrates.

There are two interesting methods of recovering additional foodstuffs of good quality: 1) recovery of glycerin by hydration or hydrogenolysis of synthetic monosaccharides and subsequent use thereof as carbohydrates in the diet of animals and man; 2) conversion of synthetic carbohydrates into organic acids, which could serve as the nutrient medium for cultivating yeast, which is valuable food protein for animals and man.

It is common knowledge that microorganisms can utilize organic acids as a source of carbon. This capacity depends on the species, strain of organism, individual acid used and its concentration in the medium, composition of the medium, pH, etc. [3].

Organic acids themselves have much practical importance to the chemical industry, where they are presently being produced either from expensive comestible products of fermentation of sugars by means of bacteria (butyric, lactic, acetic fermentation, etc.) or they are recovered from natural sources (higher fatty acids, citric acid and others) using time-consuming technological processes.

It is known that monosaccharide stability is quite high in solutions of natural sugars with neutral reaction (particularly acid) [4]. In an alkaline medium, monosaccharides undergo a number of complicated conversions. In a mild alkaline solution there may be dissociation of sugar molecules, which is associated with formation of numerous products, mainly hydroxy acids (glycolic, glycerinic, trioxybutyric, lactic, saccharinic and others).

Under certain conditions (shortage of oxygen and others), monosaccharides are decomposed by alkali with predominant formation of lactic acid (up to 70% and in some cases more) [5]. The presence of an alkaline medium can be viewed as a sort of "activation" of sugar [4], which enhances oxidative processes. However, we do not know of any works in the literature that deal with the process of recovering organic acids from monosaccharide racemates for the purpose of subsequent use in life support systems.

Our objective here was to explore the possibility of obtaining nontoxic substances (organic acids) from monosaccharide-racemates condensed from formaldehyde that was synthesized from human waste by the scheme described above. In addition, we studied the possibility of analysis and purification of synthetic acids.

Methods

Synthetic monosaccharide carbohydrates were recovered from a formaldehyde solution in the presence of inorganic catalyst $Ca(OH)_2$ (optimum proportion) at high temperature. When left at such a temperature for a long time in an alkaline medium, synthetic monosaccharides break down into organic acids. Experiments were conducted in glass containers, with continuous mixing in an incubator, at a temperature of +50°C and atmospheric pressure in the presence of $Ca(OH)_2$ catalyst. The composition of the reaction medium was as follows: 4% formaldehyde, $Ca(OH)_2$ catalyst 2%, water 94%, and total of 100 ml mixture.

We used the sulfate method to determine the amount of formaldehyde in the reaction mixtures [6]. We first assayed total sugars by the method of Maken and Shoori [7]. Total acidity, or total acid content referring to total anions and nondissociated molecules of acid, was determined by the method mentioned by B. P. Pleshkov [8].

We used the method of A. N. Belozerskiy to isolate non-volatile acids (lactic and butyric) from the solutions [9]. Since condensation of formaldehyde into carbohydrates and dissociation of the latter to acids occurred in the presence of $Ca(OH)_2$, the calcium salts of these acids were precipitated from the mixture by adding 4 volumes of 96% ethyl alcohol. We took 100 ml of the initial solution of synthetic acids for analysis, and added 400 ml 96% ethanol. The precipitate (calcium lactate and butyrate) was acidified according to Congo red with sulfuric

acid, and solution extracted with ether in a separating funnel. When the ether solution thickened to a dry state, a thick oily lactic acid fluid was obtained with crystals of butyric acid.

For qualitative analysis of the mixture of organic acids obtained from acidulation of synthetic monosaccharide carbohydrates we used the method of ascending paper chromatography [9, 10]. The acids were separated in a system of solvents: n-butyl alcohol--formic acid--water (13:2:9) on brand C chromatography paper. Standard acid solutions (0.1 M) served as markers. The acids were separated in 24 h.

After drying the chromatograms in a stream of air for 20 min at 20°C, then in a dryer for 2 h at 60-30°C, the acids were developed using 0.05% alcohol solution of bromphenol blue. Organic acids were developed in the form of yellow spots on a light blue background. The entire experiment lasted 24 h.

Results and Discussion

As a result of condensation, monosaccharide carbohydrates are formed from formaldehyde (up to 32% mass of initial formaldehyde). Then the synthetic monosaccharides are completely converted into organic acids. The total amount of acids is the sum of acids formed in the Cannizzaro reaction and upon dissociation of monosaccharides.

Quantitative and qualitative analysis of the mixture of synthetic acids obtained in an air atmosphere revealed that 15% of them consist of lactic and succinic acids.

Paper chromatography of the mixture of synthetic organic acids obtained in an air atmosphere revealed that it contains succinic, oxalacetic, citric, malic, tartaric, acetic, malonic, maleinic, fumaric and unidentified high molecular acids close to the start line.

Organic acids were also obtained by the above-mentioned methods from synthetic monosaccharides in an atmosphere of nitrogen and oxygen (separately).

Total amount of synthetic monosaccharides and organic acids in reaction mixtures with different gas atmospheres

Gas atmosphere of reaction (condensation of CH_2O into carbohydrates and conversion of latter into acids	Total sugar, g/100 ml	Sugar yield, % of CH_2O used in reaction	Total acid content, g
Air (control)	1.668	44.5	3.21
Nitrogen	1.640	44.8	3.14
Oxygen	1.007	27.7	2.82

Fewest sugars were formed in an oxygen atmosphere. Apparently, in this case, there was the most complete Cannizzaro reaction. In all cases, total amount of acids remained at the same level. In an oxygen atmosphere, there was prevalence of formic acid in the mixture, which was formed in the Cannizzaro reaction (see Table).

The results of chromatographic analysis revealed that the qualitative composition of organic acids in different gas atmospheres was virtually the same, there being a significant increase in lactic and succinic acids in the case of recovery of organic acids in a nitrogen atmosphere.

Acids were recovered from glucose, fructose, xylose and mixtures thereof in order to compare the compositions of mixtures of organic acids formed from synthetic and natural monosaccharides. For this purpose, we added to the reaction mixture 1.6 g natural monosaccharide. This was the mean quantity of synthetic monosaccharides formed in the condensation reaction from 4 g formaldehyde in the presence of 2 g $Ca(OH)_2$. The reaction of acidulation of natural monosaccharides was run in an alkaline medium and air atmosphere. The results of chromatographic analysis revealed that each of the monosaccharides receives the same set of organic acids: oxalic, succinic, malonic, maleic, citric, tartaric and lactic. Comparative chromatographic analysis established that lactic, citric and maleic acids are formed in lesser quantities in the case of conversion of natural monosaccharides than with oxidation of synthetic carbohydrates, whereas acetic, fumaric and malic acids are not formed at all.

Since the synthetic organic acids were present in solution in the form of calcium salts, it is necessary to remove calcium in order to recover pure acid solutions.

We made a preliminary attempt to remove calcium ions from the mixture of synthetic acids by means of electrodialysis with the type AO-1 instrument used to desalinate biological fluids. We used MA-40 diaphragms in the OH^- form and MK-40 in the H^+ form. As a result of electrodialysis, the calcium ions were completely removed from the solution of synthetic acids.

Preliminary experiments involving cultivation of yeast in mixtures of synthetic organic acids were conducted for biological evaluation of these acids.*

The experimental data revealed that there was intensive growth of yeast of the species Candida tropicalis CK-4 when mixtures of synthetic organic acids were used as a carbon source.

It was established that this culture yields a good increment of biomass with the use of citric, lactic, acetic, malic, tartaric, formic, adipinic, malonic and oxalic acids. In this case, the yield of yeast exceed the amount of biomass produced on the control Rieder medium.

Future studies in the field of physicochemical recovery of synthetic organic acids should include development of methods for isolating different acids from mixtures or selective synthesis of specific acids (for example, lactic).

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EFFECT ON MOUSE SKIN OF RADIATION DIFFERING IN LINEAR ENERGY TRANSFER

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 63-65

[Article by N. Ya. Savchenko, A. I. Portman and N. I. Ryzhov, submitted 12 Apr 79]

[English abstract from source] Experiments were carried out to measure the time and severity of the radiation reaction of the skin of mice exposed to X- and gamma-radiations, protons with energies of 645 and 50 MeV as well as accelerated helium ions at doses of 200 to 4000 rad. It was found that relative biological effectiveness coefficients of 645 and 50 MeV protons were 1.0 and those of helium ions were 1.3 for the skin reaction at early and late stages of observation. No significant difference in time of manifestation of radiation-induced skin lesions related to radiations with various LET was detected.

[Text] The high density ionizing component of radiation may make a significant contribution to the radiation dose to superficial tissues of the body during long-term space flights [1]. According to existing data, the acute cutaneous reaction was more severe under the effect of radiation with high linear energy transfer (LET) than x- or gamma radiation [2-5]. There is extremely little information in the Soviet literature concerning the effects of heavy charged particles differing in LET on the skin of animals or man.

Our objective here was to determine the quantitative relationship between dosage, type of radiation and severity of radiation lesion to mouse skin after single exposure to x- and gamma radiation, 645 and 50 MeV protons and accelerated helium ions with energy of 8 MeV/nucleon.

Methods

Experiments were conducted on 114 noninbred white mice and 76 CBA×C$_{57}$Bl$_6$ (F_1) hybrid mice weighing 18-20 g. Severity of clinical reaction graded in points (Table 1) and extent of damage to hair follicles [6, 7] served as criteria in evaluating the condition of the skin. The animals were exposed to local radiation in doses of 200 to 4000 rad. Nonirradiated skin sections of experimental animals and animals exposed to gamma and x-radiation served as a control. Irradiation conditions for control groups were as follows: x-radiation, 200 kV, 15 mA, with copper (2 mm) and aluminum (0.5 mm) filters, focus-skin distance (FSD) 30 cm, dose rate 1.5 rad/s; ^{60}Co gamma radiation at a dose rate of 9 rad/s. In the case of

x-radiation, the trunk of the animal (with the exception of the right hind leg) was protected with a lead shield (1 cm thick); the walls of a large steel collimator served as such a shield with the use of protons. The dose rates of protons, with energies of 645 and 50 MeV, constituted 10 and 0.5 rad/s, respectively and that of accelerated helium ions was 10 rad/s. Prior to irradiation, we shaved the white mice and used only animals without visible lesions to the skin or hair growth. The area of the experimental skin section was about the same in all cases and did not exceed 1.5 cm^2. We assessed the clinical reaction of the skin to radiation for 105 days after exposure.

Results and Discussion

The results of this study were indicative of development of a marked radiation lesion to the skin, which appeared in the mice after exposure to x-rays, 645 and 50 MeV protons, as well as helium ions. The acute cutaneous reaction to the tested forms of radiation in doses of 300 to 4000 rad can be defined as erythema, dry and exudative dermatitis. The severity of radiation lesion to the skin under the influence of radiation with LET in the range of 0,2 to 22 keV/μm was a function of dosage. Mathematical processing of the obtained data revealed that the dose-effect function for skin can be described satisfactorily in the form of regression equations for the tested forms of radiation (Table 2). A comparison of the coefficients of slope of the lines of regression for helium ions and x-rays demonstrates the significance of differences between them, which is indicative of the desirability of using the isolated or mean value of the coefficient of relative biological effectiveness (REB) in determining the biological effectiveness of helium ions, i.e., with this form of radiation REB is not a function of dose level. A comparison of equieffective doses of x-rays, protons with different energies and helium ions revealed that the REG of protons with energies of 645 and 50 MeV are close to 1.0 for the erythemic skin reaction, dry and exudative dermatitis; the REB for helium ions is 1.3. In view of our data and the results of other studies of the effects of heavy charged particles on animal skin, it can be concluded that REB have a tendency toward increasing from 1.0 to 3.0 with change in LET from 0.2 to 155 keV/μm [2-5].

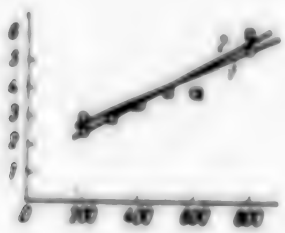
Table 1. Scoring scale for radiation reactions of the skin

Radiation reaction of skin			
injury phase		recovery phase	
0.0	No difference from nonirradiated skin	0.0	No difference from nonirradiated skin
0.5	Erythema	0.5	Growth of some hair
1.0	Erythema, edema	1.0	Marked epilation, thinned and dry skin
1.5	Erythema, edema, scales	1.5	Marked epilation, shiny edematous skin
2.0	Exudative sloughing of epidermis in some parts of irradiated surface	2.0	Some areas of exudative sloughing of epidermis, formed scab
2.5	Exudative sloughing of epidermis over half the irradiated surface	2.5	Small unhealed areas
3.0	Exudative sloughing of epidermis over most of irradiated skin surface, small ulcerations	3.0	Extensive unhealing surface
3.5	Necrosis of irradiated surface		

Table 2.
Equations of regression for experimental data obtained after single local exposure of mouse skin to radiation differing in LET

Type of radiation	LET, keV/μm	Regression equations
X-radiation	0.2	$y = (0.43 \pm 0.04)x$
Protons, 645 MeV	0.2	$y = (0.45 \pm 0.07)x$
Protons, 50 MeV	1.2	$y = (0.43 \pm 0.04)x$
Helium ions	22.0	$y = (0.56 \pm 0.05)x$

Key:
y) cutaneous effect expressed in probit units
x) dose (rad)



Damage to hair follicles after exposure to protons with energy of 50 MeV (1) and ^{60}Co γ-rays (2). X-axis, dose (rad); y-axis, severity of lesion (arbitrary units)

A comparison of the dynamics of manifestation of mouse skin reaction after exposure to protons with energy of 645 and 50 MeV, helium ions and x-radiation failed to demonstrate reliable differences in time of formation of radiation lesion. In the case of x-rays, as well as protons and helium, in doses of 300-4000 rad, the first symptoms of radiation lesion to the skin appeared on the 5th-8th postradiation day, with development of maximum radiation reaction on the 14th-22d day. In all cases, the acute manifestations of irradiation of the skin terminated on the 30th-35th postradiation day. On the basis of the obtained data concerning time of onset, rate of progression, maximum manifestation and subsequent regression of radiation reactions, we see that development and course of processes of damage and recovery in irradiated skin were the same after exposure to radiation differing in LET.

Clinical findings with regard to the effectiveness of protons with energy of 50 MeV for the skin conform well with the results obtained from assessing the condition of the skin according to severity of damage to hair follicles: RBE of protons also constituted 1.0 according to this criterion (see Figure), i.e., we see that the biological significance of protons with energy of 50 MeV for the skin remains constant over a rather wide range of doses (from 200 to 4000 rad) and with the use of various criteria to evaluate the condition of the skin.

The manifestations of the skin's reaction to radiation, assessed 3.5 months after exposure to protons with energy of 645 and 50 MeV consist essentially of development of atrophy and epilation. REB of protons with different energies constituted 1.0 for the reaction of white mouse skin at the late postradiation stages.

Thus, mice developed a marked radiation lesion to the skin, the severity of which depended on dosage and LET of radiation, under the influence of x-rays, protons with energy of 645 and 50 MeV, as well as accelerated helium ions. RBE of protons with energy of 645 and 50 MeV was close to 1.0 for the skin reaction to radiation at the early (30 days) and late (105 days) observation stages over the entire range of tested doses (200 to 4000 rad). RBE of helium ions constituted 1.3 in the dose range of 300 to 4000 rad. A comparison of the dynamics of manifestation of the skin reaction to radiation differing in LET failed to demonstrate reliable

differences in time of formation and development of the radiation lesion to the skin. Evidently, one should make use of relevant recommendations, which were worked out for standard forms of radiation with consideration of RBE of high density ionizing components, when settling questions of protection, prognosis and therapy of skin lesions after exposure to ionizing radiation differing in LET.

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EFFECT OF PERSISTENT REGIONAL VASCULAR HYPOTENSION ON GROWTH OF MALIGNANT TUMORS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 63-67

[Article by P. V. Rudenko, submitted 24 Apr 80]

[English abstract from source] Weightlessness effects on the cardiovascular system of laboratory rats were simulated by prolonged arterial hypotension. In this situation antitumor stability of the animal body increased. The effect resulted from the compensatory reactions in vessels of blastomas and adjacent tissues. It is recommended to carry out such experiments in real space flights.

[Text] Studies of different aspects of the effect of weightlessness on living organisms are needed primarily by the practice of space flights. Among the numerous aspects of this complex problem, still unstudied is the growth of malignant neoplasms under space flight conditions. Yet there are grounds to raise such a question. On the one hand, this is referable to the prospects of development of cosmonautics, which are related to performance of long-term flights when the cardiovascular system is submitted to significant factors. On the other hand, there have been reports in recent years of a correlation between state of the cardiovascular system and growth of malignant tumors [1-3]. Finally, even with the most meticulous medical screening, one cannot be certain that the future astronaut is free of asymptomatic disposition for neoplasms or even a minimal blastoma, the reaction of which to long stays in space is not known. All this serves as sufficient grounds to investigate this matter.

The above facts and considerations served as an impetus to organize studies of the distinctions of growth of transferable sarcoma 45 and Walker's carcinosarcoma in rats under conditions simulating the effect of weightlessness on the vascular system.

Methods

The absence of gravity during space flights diminishes stretch loads in vessels that are attributable to hydrostatic blood pressure. Constriction of the abdominal aorta below branching of renal arteries with a nichrome spring is one of methods of creating stable regional arterial hypotension [4]. It was demonstrated that arterial pressure (and consequently stretching loads) in great vessels below the constriction site drops by 30-50% of the base level if this is done. However, the volumetric blood flow rate, number of functional capillaries and transcapillary exchange do not change. This is possible because, by virtue of compensatory

changes that lead to a decrease in resistance in the resistive and elastic parts of the vascular system, the gradient of capillary pressure remains unchanged.

The experiment was conducted on 230 mongrel white laboratory rats of both sexes weighing 150-190 g. We induced a decrease in stretching loads to vessels of the hind part of the body by the above-described method of constricting the abdominal aorta in the experimental animals. A pseudo-operation was performed on the control group of animals. Arterial pressure was determined by measuring mean pressure in the femoral artery by the direct method. All painful manipulations and euthanasia were performed under intraperitoneal thiopental anesthesia.

In the first series of experiments, we determined the probability of formation of incipient tumor, which was evaluated on the basis of percentage of successfully transferred sarcoma 45. In the second series, we studied the growth rate, nature of morphological changes and microcirculatory system of sarcoma 45. In the third series, we recorded survival time after transfer of Walker's carcinosarcoma. In all cases, the transfer was made into the femoral muscle by the conventional methods. The obtained digital material was submitted to statistical processing.

Results and Discussion

The Table lists the summary results of our studies. As can be seen in this Table, arterial pressure in the posterior part of the body of experimental animals was an average of 40% lower than in the control.

Influence of arterial hypotension on acceptance, rate of growth of blastoma and survival time of animals with tumors

Group	Number of rats	Arterial pressure mm Hg	Successful transfers %	Tumor weight, g			Survival time, days
				after 7 days	after 14 days	after 21 days	
Control	90	98±3.6	91	3.0±0.4	7.5±1.6	12.8±2.6	13.5±0.5
Experimental	140	59±3.6	61	1.2±0.2	3.0±1.0	5.5±0.8	22.5±0.9
P	—	<0.001	<0.05	<0.001	<0.02	<0.05	<0.01

Analysis of data obtained on the group of animals in whom we studied acceptance of sarcoma 45 revealed that the probability of onset of tumor diminished when it was inoculated into tissues whose vessels experienced a diminished stretching load. This phenomenon could be attributed to the data concerning correlation between vascular reactions in the transplant site and onset of transferable tumors. According to current conceptions, inoculated cells begin to proliferate and form a tumor node only after capillaries migrate into them [5]. Since absolute pressure in the resistive part of the microcirculatory system was diminished in our experiments, the angioplastic effect of inoculated cells was attenuated, because elevation of pressure in capillaries is a direct stimulus and mandatory condition for capillary growth.

The diminished load causing stretching of vessels also affected the rate of blastoma growth. As can be seen from the data listed in the Table, growth of sarcoma 45 developing in the presence of arterial hypotension was decreased to less than one-half, as compared to the control. This slowing is also apparently related to

attenuation of antiogenic reactions of surrounding tissues, whose vessels are also hypotensive.

Survival time of experimental animals with Walker carcinosarcoma more than doubled, as compared to the control. This is indicative of the persistence of antineoplastic effect of diminished vessel-stretching loads. It is apparently due to the slower rate of blastoma growth as a result of diminished angiogenic reaction of surrounding tissues, as well as diminished mass of viable cells due to autolysis of central parts of the tumor. It was also noted that autolysis occurred as a result of discontinued blood flow in the region of the microcirculatory bed which, as we know, is incapable of compensating for the decrease in absolute arterial pressure in malignant neoplasms [3, 6].

Thus, our data are indicative of the fact that a decrease in vessel-stretching loads has a marked antineoplastic effect. The observed effect is attributable to the nature of vascular reactions in the tumor proper and surrounding tissues. It is expressed on the microcirculatory level. Since the microcirculatory system has the same structural and functional features in transferred, induced and malignant neoplasms of man, we could probably expect that the antineoplastic action demonstrated in model experiments will extent to all types of above-mentioned neoplasms.

On the basis of these studies, it can be conlcuded that long-term exposure to weightlessness is not associated with an increased risk of neoplastic pathology. However, in spite of the adequacy of the model we used, it is difficult to obtain on earth exhaustive information about the questions posed, and the general conclusion must be evaluated as being very tentative. On this basis, it is deemed expedient to pursue analogous studies during actual space flights.

It should be noted that pursuing such studies in orbit is of scientific and practical interest, not only directly to cosmonautics, but also fruitful for oncology, helping resolve basic problems and identify the intimate mechanisms of appearance and development of malignant neoplasms and, in particular, determine the effect on these processes of the state of the cardiovascular system.

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DYSTROPHIC CHANGES AND FUNCTIONAL IMPAIRMENT OF DEAFFERENTATED BONE MARROW

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 67-69

[Article by A. S. Zverkova, N. K. Simeonova, I. V. Abramenko and V. P. Sobol', submitted 28 Jul 80]

[English abstract from source] Rat experiments have shown that radicotomy of spinal cord roots at the L_2-Z_1 level causes functional disorders of bone marrow eliminating stimulation of hemopoiesis in response to acute blood losses. The deafferentiated bone marrow shows disturbed proliferation and differentiation of cellular elements and dystrophic changes in them.

[Text] We know that the anemic syndrome develops in cosmonauts who have participated in long-term space flights. Intensification of erythrocyte breakdown, hyperoxia, diminished energy requirements of the body due to hypodynamia and weightlessness are considered by researchers to be the possible interrelated causes thereof [1-6]. V. N. Shvets and V. V. Portugalov [1] use the conception of P. A. Korzhuyev [7], to the effect that the load-bearing skeleton is involved in regulation of activity in hemopoietic sites, to explain the pathogenesis of the anemic syndrome. In weightlessness, the intensity of hemopoiesis diminishes because of the inadequate load on the skeletomuscular system. Evidently, the skeleton and bone marrow are in a state of functional deafferentation under such conditions. At the same time, we know that deafferentation created surgically in experiments leads to development of a neurodystrophic process in the organ with impaired sensory innervation [8]. This can also apply to bone marrow.

Considering deafferentation as one of the possible factors in onset of the anemic syndrome in weightlessness, we tried to pinpoint experimentally the effect of deafferentation of bone marrow on its functional capacity.

Methods

Our study was conducted on 50 mongrel rats weighing 200-250 g. Neurogenic dystrophy was simulated by unilateral transection of sensory radices of the spinal cord on the level of L_2-Z_1, which caused loss of sensibility in one of the hind legs, with retention of movements on both sides. Two weeks after deafferentation, we took 1 ml blood (7% of total amount) from the carotid artery. Three days later we extracted bone marrow from the femur and prepared impression smears, which we stained according to Pappenheim. We studied the morphological distinctions of

bone marrow cells, counted the myelogram, calculated the bone marrow indexes (leukoerythroid index, index of erythroblast maturation, bone marrow neutrophil index). A comparison was made of bone marrow hemopoiesis on the side of deafferentation and contralateral side. Intact animals that were not submitted to denervation or blood-letting served as an additional control. The results were submitted to statistical processing with the use of the t criterion for paired samples [9].

Results and Discussion

Unilateral impairment of sensory innervation caused development of edema of the leg on the denervated side on the day after surgery. After 2 weeks, the muscles became atrophic, and trophic ulcers developed on the heel in half the cases. At this same time, a functional load was imposed on the bone marrow of 15 animals in the form of acute blood-letting. The reaction of deafferentated bone marrow was not the same as on the contralateral side.

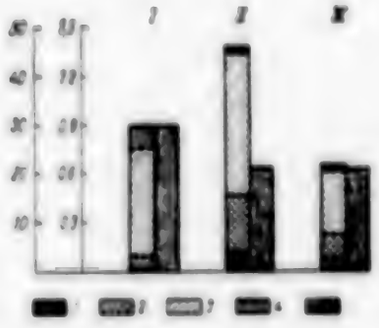

Figure 1.
Change in bone marrow erythroid reaction to acute blood-letting in the presence of deafferentation.
I-III) erythroid bone marrow elements of intact animal, after blood-letting and after deafferentation with blood-letting
1) proerythroblasts
2-4) basophil erythroblasts, polychromatophil and oxyphil, respectively
5) index of erythroblast maturation
The following is shown for each of these 3 situations: formed elements (%) on the left; index of erythroblast maturation on the right

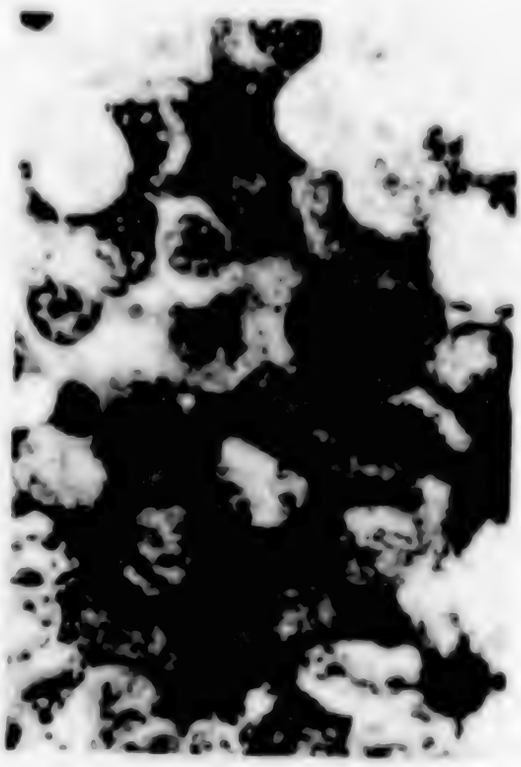

Figure 2.
Morphological changes in bone marrow elements after deafferentation and acute blood-letting. Erythroblasts with pyknotic nucleus, with megaloblast features, excessive granulation in cytoplasm and hypersegmentation of neutrophil nuclei. Pappenheim's stain; magnification 400×

Effect of deafferentation on some parameters of bone marrow hemopoiesis in rats against the background of acute blood-letting

Myelogram parameters	Bone marrow		$\bar{x}_1 \pm s_{\bar{x}_1}$
	deafferentated side ($\bar{x}_1$)	contralateral side ($\bar{x}_2$)	
Blasts, %	3.6	1.81	1.8±0.3*
Neutrophils, %	56.95	45.65	11.3±3.7*
Eosinophils, %	5.25	3.49	2.0±1.2**
Lymphocytes, %	9.95	5.24	4.7±2.6**
Plasma cells, %	1.8	1.46	0.34±0.2**
Index of neutrophil maturation	0.70	0.84	0.36±0.1**

* $P < 0.05$.
** $P > 0.05$.

In the bone marrow of the contralateral paw, we demonstrated changes indicative of a reaction of erythroid elements to blood-letting; there was an increase in amount of erythropoietic elements, as compared to the control ($P<0.05$) and decline of erythroblast maturation index--$P<0.001$ (Figure 1).

In contrast, we failed to demonstrate signs of stimulation of erythropoiesis in deafferentated bone marrow, and there were even signs of depression thereof (see Figure 1). There were fewer erythroid elements in bone marrow of the deafferentated leg than in intact animals ($P<0.1$). These differences were more marked in paired comparisons of the deafferentated and contralateral sides ($P<0.05$). The index of erythroblast maturation was lower than in intact animals ($P<0.001$).

We also demonstrated morphological changes in erythroid cells on the side of deafferentation, which were characterized by the following signs of dystrophy: erythroblasts with pyknotic nucleus, erythroblasts with megaloblast features--large, often irregular-shaped cells with wide cytoplasm and delicate alveolar structure of nucleus (Figure 2).

On the side of deafferentation there were more blast cells than on the contralateral side (see Table).

A study of morphological features of granulopoietic elements on the deafferentated side revealed dystrophic changes: vacuolization of nucleus and cytoplasm, dissociation of degree of maturation of nucleus and cytoplasm, hypersegmentation of the nucleus and condensation of its chromatin, excessive granularity and basophilia of cytoplasm in some neutrophils (see Figure 2). Bone marrow smears revealed inactive megakaryocytes wanting in azurophilic granulation. Such phenomena were observed as an exception on the contralateral side.

The results we obtained indicate that proliferation and differentiation of cellular elements are impaired, and dystrophic changes appear in the cells of bone marrow wanting in sensory innervation. Analogous findings were made by M. I. Pekarskiy [10] in experiments on cats after resection of the brachial plexus. It was found that there is impairment of functional capabilities of deafferentated bone marrow, manifested by absence of stimulation of hemopoiesis in response to acute blood-letting. These data can be used to analyze the pathogenesis of anemic states in the presence of functional deafferentation of bone marrow in weightlessness.

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UDC: 616.12-008.331.1-057:656.7-051]-072.7:616-001.12-031.22

ENDURANCE OF LOWER BODY NEGATIVE PRESSURE BY PILOTS WITH NEUROCIRCULATORY DYSTONIA OF THE HYPERTENSIVE TYPE

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 70-72

[Article by P. M. Suvorov, N. N. Artamonov, B. N. Tarnovskiy and Yu. I. Bykova, submitted 20 Jun 79]

[English abstract from source] Cardiovascular function and LBNP tolerance were studied in 68 pilots with hypertensive neurocirculatory dystonia and 26 healthy test subjects (controls). The studies demonstrated that most dystonic subjects had distinctly peculiar features of cardiovascular compensatory reactions during LBNP tests and that 86.8±4.1% of them showed high tolerance to the exposure. Their cardiovascular function was compensated at the expense of a greater than in the controls increase in the arterial tone. There were, however, fairly many cases (13.2±4.1%) who displayed failures of cardiovascular compensatory reserves and who lost the ability to maintain long a high arterial tone in response to the exposure. The use of provocative tests is the only method that can help identify compensatory capabilities of the cardiovascular system of pilots with hypertensive neurocirculatory dystonia and thus qualify them for their professional activities.

[Text] Hypertensive neurocirculatory dystonia (HND) and essential hypertension are in first place among cardiovascular diseases that lead to disqualification of young flight personnel, and they have shown a distinct tendency toward increasing in frequency in the last decade [1-3]. In spite of the numerous studies conducted in this area [4-9], many questions of etiology and pathogenesis of this disease are still unclear. Our objective was to examine the tolerance by individuals with HND of a functional test involving decompression of the lower half of the body (LBNP), which is used in expert medical certification of flight personnel to demonstrate a predisposition for syncopes [10].

Methods

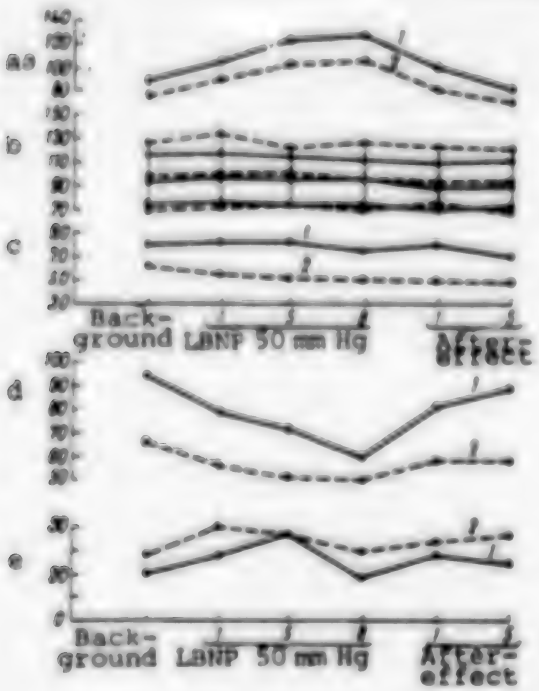
We conducted our studies in a decompression chamber with the subject in sitting position and his body immersed in a vacuum compartment to the level of the upper crests of the iliac bones. We used negative pressure (in relation to outside barometric pressure) of -50 mm Hg, with exposure for 8 min. In the course of the examination, we recorded the electrocardiogram, tachooscillogram of the brachial artery, sphygmogram of the carotid and femoral arteries. We calculated systolic

(SV) and minute (MV) blood volumes with the formula of Bremser-Ranke, and used the method of N. N. Savitskiy to determine specific peripheral resistance (actual and working) and ratio between them as a percentage, which enabled us to assess the intensity of arterial vascular tonus. In the LBNP tests, appearance of relative sinus bradycardia (slowing of pulse rate by 20 or more per min), drop of lateral systolic pressure to 90 mm Hg or less and drop of pulsed pressure to 20-25 mm Hg or less were the main criteria of signs of decompensation of cardiovascular system functions. We also took into consideration several additional signs of lack of tolerance of the test (feeling of weakness, discomfort, pallor of the facial integument or hyperhidrosis).

We conducted these studies on 68 pilots with HND and 26 healthy subjects (control group) of an analogous age, who had about the same tenure in flight work. The obtained data were processed by methods of variation statistics.

Results and Discussion

We found lower tolerance of the LBNP test in individuals with HND than in healthy subjects. In particular, 9 (13.2±4.1%) out of the 68 pilots with HND showed poor tolerance (endurance fluctuated from 5 to 7 min), whereas in the control group diminished tolerance of decompression was found in only one subject (3.8±3.7%). This difference in endurance of decompression between the groups studied is close to statistical reliability ($t = 1.92$).



Main hemodynamic parameters of pilots with HND and healthy subjects under the influence of LBNP

a) pulse rate (per min)
b) arterial pressure (mm Hg)
c) MV (ℓ/min)
d) SV (mℓ)
e) arterial vascular tonus (% of nominal value)
1) healthy subjects
2) subjects with HND

Analysis of physiological reactions of pilots with HND (with good tolerance of the test) enabled us to demonstrate some specific distinctions of their hemodynamic state (see Figure): lower heart rate throughout the study ($P<0.05$), higher systolic arterial pressure ($P<0.05$), lower SV and MV. Minimum and mean arterial pressure of the group under study did not differ appreciably from the control in most cases ($P<0.05$).

Intensity of vascular arterial tonus was somewhat greater in subjects with HND than in the control group. Statistically significant differences ($P<0.05$) were noted in the background, 1st and 8th min of LBNP.

Our data conform in essence with the studies of G. F. Lang [4] and A. L. Myasnikov [5], who demonstrated that constriction of arterioles of a generalized nature is of decisive significance to elevation of arterial pressure in the presence of essential hypertension. However, as shown by our data, in addition to generalized arteriolar spasm (70% of the cases) with normal or low MV in subjects with HND, there may be other hemodynamic correlations. In particular, in 20% of the individuals with HND, elevation of systolic blood pressure was due to above normal MV. In 10% of the pilots with HND, MV and arterial vascular tonus did not exceed the range of normal fluctuations ($M \pm 2m$) in healthy subjects, but were close to the top limit.

As indicated above, 9 out of the 68 pilots with HND demonstrated poor endurance of decompression. Analysis of their physiological reactions revealed that the main hemodynamic parameters did not differ appreciable from those of subjects with good endurance in the initial state and 1st min of decompression ($P<0.05$). In the middle of the exposure period, before development of a critical state (in the 3d min on the average) individuals with poor endurance of decompression developed a drastic decrease in arterial vascular tonus (to $17 \pm 4\%$, versus $33 \pm 2\%$ in individuals with good tolerance). This created favorable conditions for deposition of circulating blood in the lower half of the body, diminished return thereof to the heart, which led to a drop of SV and MV ($P<0.01$) and level of mean arterial pressure ($P<0.05$). Pulse rate, lateral and minimum pressure did not differ with statistical reliability at this time, as compared to the group with good tolerance. One minute prior to development of a critical state, in addition to diminished intensity of arterial vascular tonus, SV and MV, there was slowing of pulse and decline of all parameters of arterial pressure ($P<0.001$). In the aftereffect period, individuals with HND and low tolerance of the test continued to present lower heart rate ($P<0.001$) and SV.

Thus, according to the results of the LBNP tests, $13.2 \pm 4.1\%$ of the pilots with HND presented unstable regulation of arterial tonus, manifested by diminished intensity thereof, which led to development of decompensation of the cardiovascular system and worsening of general well-being.

The above distinctive feature in regulation of vascular tonus of individuals with HND must be reflected in the diagnosis of the disease and expert decision. One should make a negative expert decision only in cases of low tolerance of repeated functional tests.

The foregoing is indicative of the desirability of broader use of the LBNP test in the practice of expert medical certification of pilots.

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QUANTITATIVE EVALUATION OF CLINICAL MANIFESTATIONS OF MOTION SICKNESS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 72-75

[Article by R. R. Galle, submitted 26 Sep 80]

[English abstract from source] An original scheme of quantitative evaluation of clinical manifestations of motion sickness has been developed. According to the scheme, eight major symptoms of motion sickness: vertigo, nausea, vomiting, sweating, paleness, headache, sleepiness, flaccidity are scored in relation to their manifestations. The scheme has been used in vestibular tests of 57 test subjects. The vestibular test used is tolerance to cross-coupled acceleration. On the basis of the scores quantitative criteria of human tolerance to vestibular exposures have been suggested. It is emphasized that the scheme can be widely used allowing statistical treatment, comparative individual and group analysis of the data obtained.

[Text] Motion sickness is characterized by symptoms, in the development of which many functional systems of the body are involved [1]. The severity of the symptoms of this disease fluctuates over a wide range, from barely perceptible sensations to severe manifestations. All this makes it difficult to make a comparative clinical evaluation of motion sickness, which was reduced until recently to listing the symptoms and verbal description of their severity.

Such categories of evaluation as seasickness [2], severity of vestibulovegetative reactions [3] and giving a grade to statokinetic stability [4] are qualitative, and they do not fully meet current requirements of studies of the problem of motion sickness, particularly in connection with the increased interest in the space form of the disease, which is one of the pressing problems of space medicine [5].

In the last few years, there has been a tendency to give a quantitative description of the clinical manifestations of motion sickness. American authors have described in detail a comprehensive system for grading the severity of motion sickness [6], and they use it extensively to analyze endurance of various vestibular factors. However, in their system, such symptoms as vertigo, headache and listlessness are relegated to a secondary place, which does not conform with the opinion of other researchers who have studied the symptomatology of motion sickness [1, 3, 7, 8 and others].

System for grading severity of symptoms of motion sickness

Symptom	Grade for severity		
	1 (mild)	2 (moderate)	4 (severe)
Vertigo	Barely noticeable, indistinct	Distinct, but not severe or impairing general condition	Severe, to the extent of disorientation worsening general condition
Nausea*	Vague discomfort, heavy or empty feeling	Slight nausea	Distinct nausea, regurgitation, hiccups
Perspiration	Moist palms and forehead	Distinct wetness of palms, sweat beads on forehead	Profuse (sweat running down face, back)
Facial pallor	Mild	Moderate	Marked
Headache	Sensation of heaviness, compression, bursting and other unpleasant sensations in the head	"	"
Sleepiness	Readily overcome sleepiness, with occasional yawning	Moderate desire to sleep hindering work, frequent yawning	"
Listlessness, apathy	Some decrease in interest in performing work	Moderate inertia, no interest in working	Total indifference toward any assignment or surroundings
Others (sensation of heat, cold, facial hyperemia, salivation, dry mouth, dyspnea, fatigue, etc.)	Each symptom scored 1 point, regardless of severity	--	--

* Vomiting episode is scored an 8.

We submit here a system for quantitative evaluation of severity of motion sickness with consideration of the chief and additional clinical symptoms, as well as the results of using it to assess endurance of the well-known test for cumulative Coriolis accelerations or, more precisely, precession accelerations [9].

Methods

A total of 57 essentially healthy male subjects participated in these studies; they ranged from 23 to 35 years in age.

The studies involved the use of a revolving chair that turned at the rate of 30 r/min. In one round, which lasted 1 min, the subject had to bend forward at the waist 4 times while seated with his eyes closed, at the pace of 1 movement per 3 s and with 5-s intervals between bends. After a 1-min break, the subject repeated these movements with the chair turning in the opposite direction.

The test involved no more than 15 rounds of rotation, and was stopped prematurely if nausea or marked signs of motion sickness appeared in two successive rounds. During the rotations, we observed the condition of the subject, and in the intervals between rounds we assessed the severity of motion sickness symptoms using a special grading system. The obtained data were submitted to statistical processing.

Results and Discussion

All of the subjects were divided into three groups on the basis of the results of observing them and their accounts of endurance of the test. The first group (5 men) consisted of individuals who endured 15 rounds of rotation with virtually no impairment of well-being, or with insignificant signs of motion sickness; the second consist of those (8 people) who endured 15 rounds with moderate signs of motion sickness (grade II vestibulovegetative reaction--VVR-2, according to the scheme of K. L. Khilov [3], and the third (44 people) were subjects with overt signs of motion sickness (VVR-3). In 19 men, the progression of signs of motion sickness was very intense and ended with an access of vomiting. It is important to note that, starting with the third round, the number of subjects in this group was reduced because of onset of marked symptoms of motion sickness. Only 13 out of the 44 men continued the test after the 5th round, and only 4 endured 10 rounds.

We used a system of scoring clinical symptoms of motion sickness to give a quantitative description of the severity of sickness (see Table).

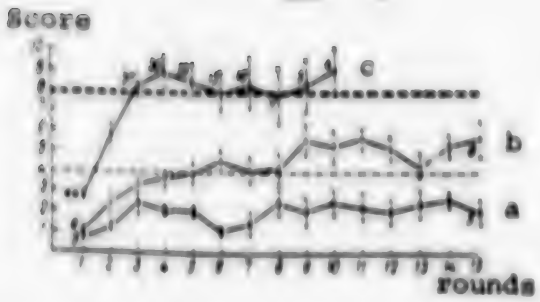
This system is based on the seven most typical symptoms of motion sickness: vertigo and illusory sensation of motion, nausea (including vomiting), perspiration, pallor, headache, sleepiness and listlessness (apathy). We arbitrarily selected a point scale reflecting three degrees of severity for quantitative grading of each of the main symptoms of motion sickness: a mild symptom was given a 1, moderate or severe--2 or 4, respectively; access of vomiting as a manifest symptom was scored an 8.

This system also took into consideration additional symptoms observed with motion sickness, along with the principal ones: sensation of heat or cold, hyperemia of the face, increased salivation, dryness of the mouth, dyspnea, fatigue, general malaise and others. The presence of each of the additional symptoms, regardless of severity, was given 1 point.

In the course of interrogating a subject following this system, we determined the severity of a symptom and gave it the appropriate grade. The quantitative description of the clinical syndrome of the disease as a whole was obtained by adding the scores for all symptoms.

The changes in score given the syndrome of motion sickness, illustrated on the curves (see Figure), showed rather graphically the differences in dynamics of each of the three groups, and they were reliable throughout virtually the entire test.

The average score for motion sickness was less than 4 in the first group for all 15 rounds of rotation, ranging mainly from 1.0 to 2.5 (curve a). This group of subjects did not actively complain of poorer well-being and rated their endurance of rotation as good; when questioned by our plan they presented 1-3 mild symptoms of motion sickness.



Dynamics of motion sickness in test with cumulative precessior accelerations (scores). X-axis, round of rotation; y-axis, grade given to motion sickness (M+m). a, b and c refer to 1st, 2d and 3d groups of subjects, respectively. The numbers above the curves indicate number of subjects.

In the second group of subjects we noted constant rise of mean score. Starting with the 6th min of the test, the score exceeded 4; however, it remained under 8 points to the end of the test. These subjects developed several moderate and mild symptoms of motion sickness. They rated their endurance of the test as satisfactory.

All of the subjects in the third group observed overt worsening of well-being during the test, which they related to onset of marked symptoms of motion sickness. The curve describing the dynamics of the grade for motion sickness in the third group rose steeply, crossing the 8-point level in the 3d min and remaining there to the end of the test.

As shown by these results, one can use scoring of severity of clinical manifestations of motion sickness to obtain quantitative criteria of man's endurance of vestibular stimuli. A score of 0 should be interpreted as an indicator of excellent endurance.* A score of 1-4 is indicative of good endurance and 5-8 of satisfactory endurance of vestibular stimuli. A score in excess of 8 is a criterion of poor endurance. Similar criteria have been proposed to evaluate the severity of seasickness [10].

At the present time, a 10-min test of cumulative precession accelerations is used in Soviet expert medical certification of flight personnel to assess endurance of vestibular stimuli. The results of this study warrant the conclusion that one can predict subsequent endurance of the test on the basis of grading the motion sickness syndrome for the first 3-4 min.

Thus, the submitted results confirm the desirability of quantitative grading of the clinical syndrome of motion sickness on a point scale, as well as the validity of the selected ranges of severity.

The method of quantitative (grade) evaluation of clinical manifestations of motion sickness, which was developed and tested in endurance tests referable to cumulative precession accelerations, may find application in the most varied situations, where it is necessary to determine the severity of motion sickness and track its dynamics. No special skill is required to learn this grading method, so that it can be used for self-evaluation of the syndrome of motion sickness under certain conditions (for example, during a space flight).

Our method of grading motion sickness yields objectivized quantitative data, which are suitable for statistical processing and permit comparative, dynamic analysis of manifestations of motion sickness in different groups of individuals under different conditions.

*There were no men with excellent endurance in the group studied.

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EVALUATION OF METHODS FOR MINERALIZING RECYCLED POTABLE WATER USING A CONDUCTOMETER

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 75-78

[Article by S. V. Chizhov, Yu. Ye. Sinyak, M. I. Shikina and T. I. Luzina, submitted 26 Dec 78]

[Text] One of the main tasks in creating systems of water supply for space flights is to develop methods of ongoing monitoring of the quality of water recycled from waste. It is known that water regenerated by different methods from waste is close in composition to distilled water, and that it is wanting in organoleptic properties and minerals. To correct the mineral composition and improve organoleptic properties of water, several methods have been proposed to enrich it with macro- and trace elements (calcium, magnesium, fluorine, iodine, chlorides, sulfates, etc.). Among them, a prominent place is occupied by method of enriching water by means of dispensing measured amounts of salt solutions, natural and synthetic minerals and ion exchange [1].

When recycling water during operation of water supply systems, it becomes necessary to use operational methods of monitoring the quality of its mineral composition. There are data in the literature concerning the use of conductometry to evaluate natural water and detect various changes in its salt composition [2]. M. P. Beysova [2] described a means of determining mineralization of natural water on the basis of specific electric conductivity with the use of group coefficients of mineralization. The coefficient links the level of electric conductivity and dry residue of waters that are similar in mineral composition:

$$K = \frac{X}{M}$$

where K is the coefficient of mineralization, in Cm/(cm·g) [Cm=coulomb?], X is specific electric conductivity (in Cm/cm) and M is mass of dry residue (in grams). It is believed that one can assay dry residue with accuracy of ±6.1% in natural waters by means of the coefficient of mineralization, according to electric conductivity [3].

V. M. Skuratov [4] established the correlation between specific electric conductivity and level of artificial mineralization of recycled water. According to the data of V. M. Skuratov, electric conductivity of potable water constituted $[3.58\pm0.97\ (3.38\text{-}3.77)]\cdot10^{-4}$ Cm/cm with mineral salt concentration of 63.69±2.7 (58.30-69.08) mg/l. In his work, it was demonstrated that one can determine

Comparative data on hardness and dry residue in enriched recycled water, obtained by experimental methods and by estimation

Method of artificial mineralization	Electric conductivity X_m Cm/cm·10^{-5}	Group coefficient $\kappa_m = \frac{X_m}{M_m} \cdot 10^{-4}$	Group coefficient $\kappa'_m = \frac{X_m}{H_m} \cdot 10^{-4}$	Dry residue, mg/ℓ: experimental M	Dry residue, estimated $M = \frac{X_m}{\kappa_m}$: κ_1	κ_2	κ_3	κ_4	Hardness, mg-eq/ℓ: experimental H	Hardness, estimated $H = \frac{X_m}{\kappa'_m}$: κ'_1	κ'_2	κ'_3	κ'_4
Dolomite [D]	2,74	0,209	8,9	14,04	13,1	15,2	15,4	15,2	0,32	0,31	0,26	0,20	0,18
D+villiaumite	4,88	0,254	10,9	18,9	19,2	27,1	27,5	27,1	0,45	0,45	0,46	0,25	0,11
D+fluorite	4,09	0,177	9,9	23,0	23,1	22,7	23,1	22,7	0,40	0,44	0,39	0,30	0,26
MP-16	10,47	0,120	10,54	81,3	87,0	58,0	59,1	58,1	0,98	0,99	0,99	2,3	0,67
MPU-6	13,00	0,178	11,3	76,0	73,1	71,8	73,5	72,2	1,20	1,15	1,23	0,75	0,83
MPU-5	30,87	0,147	11,59	220,0	210	171,5	175,0	171,0	2,80	2,67	2,94	1,6	19,7
Multicomponent salt solutions	189	0,20	23,6	873,4	945,0	1044	1057,0	994,0	8,0	8,0	17,0	9,07	12,1
	100	0,18	21,0	565,8	555,6	552,1	565,3	556,6	4,76	4,7	9,5	4,81	6,38
	79,3	0,20	24,0	397,0	397,0	738,1	448,0	441,0	3,3	3,3	7,5	3,81	5,06
	35,6	0,17	18,9	209,0	209,0	196,9	201,0	197,7	1,88	1,8	3,3	1,71	2,38
	18,56	0,17	20,2	110,2	109,0	102,5	104,9	103,2	0,92	0,92	1,7	0,89	1,19
	8,20	0,14	16,9	59,0	58,6	41,5	46,3	45,6	0,48	0,48	0,77	0,39	0,52

the level of artificial mineralization of recycled water with accuracy of ±7.3% using the mean coefficient of mineralization 0.058±0.001 (0.056 0.060) according to level of specific electric conductivity. However, it must be borne in mind that in that study artificial mineralization of recycled water referred only to the sum of concentrations of calcium, chloride and sulfate ions, rather than parameters of hardness (H) and dry residue. This does not give the grounds for using the obtained data with sufficient degree of accuracy to assay in recycled water such conventional parameters of the State Standard as dry residue and hardness of water. Moreover, in [4] water was tested that was enriched only by menas of the MP-16 mineralizer, whereas other effective methods for artificial mineralization of water were not tested by the conductometry method. For this reason, in our study here our objective was to demonstrate the correlation between specific electric conductivity and indicators of dry residue and hardness of water enriched with macrominerals and trace elements using a several methods.

Methods

For artificial mineralization of recycled water, we used the following: natural minerals--dolomite [$CaMg(CO_3)_2$], villiaumite (NaF) and fluorite (CaF_2); MP-16, MPU-5 and MPU-6 synthesized at the Scientific Research Institute of Plastics, which are minerals based on plasticized materials containing ions of calcium, magnesium, sulfates, carbonates, fluorine in specific proportions and multicomponent salt solutions ($NaHSO_4$, $MgSO_4 \cdot 7H_2O$, $CaCl_2 \cdot 6H_2O$, KI, $NaHCO_3$, $KHCO_3$, NaF). To enrich the water with salt solutions, we prepared successive dilutions, which enabled us to obtain water with hardness rated at 8.0, 4.76, 3.3,

1.88, 0.92 and 0.48 mg-eq/ℓ for solutions No 7, 8, 9, 10, 11 and 12, respectively (see Table). Enriched water (for example, with hardness of 1.88 mg eq/ℓ) contained ions in the following concentrations: Ca 26, Mg 42, Cl 62.5, SO_4 14.4, K 8.3, Na 53.5, I 10 and F 1.0 mg/ℓ. In the other samples of enriched water, the levels of these components were changed proportionately. Granulated minerals were loaded separately in glass columns (column diameter 10 mm, height 50 cm, charge 10 mℓ, granule size 2-7 mm). We passed water regenerated from a condensate of atmospheric moisture through the columns at the rate of 50 mℓ/h. We determined total hardness and dry residue in the samples of enriched water by conventional methods [5], as well as electric conductivity with the Impulse laboratory conductometer. On the basis of experimental data obtained from analysis of 10 samples of water enriched by each of the above-mentioned methods, we obtained mean statistic indicators of hardness, dry residue and electric conductivity, and used formulas to calculate the mean group coefficients of mineralization according to dry residue ($K_m = X/M$, where X is electric conductivity and M is the dry residue) and hardness ($K'_m = X/H$, where X is electric conductivity and H is hardness). On the basis of the obtained mean coefficients of mineralization and mean statistical data for electric conductivity, we calculated the parameters of hardness (H) and dry residue (M) with each method of artificial mineralization:

$$\left(M' = \frac{X}{K_m};\ H' = \frac{X}{K'_m}\right)$$

To determine the accuracy of the conductometric method of estimating the hardness and dry residue in water, we calculated the mean error of measurement, as compared to experimental data, using the following formulas:

$$\frac{M_e - M'_p}{M_e} \cdot 100\% \text{ and } \frac{H_e - H'_p}{H_e} \cdot 100\%$$

where M_e and H_e are parameters of dry residue and hardness of water determined by conventional analytical methods [5], M'_p and H'_p are the same parameters calculated from the values for electric conductivity of water.

In order to determine whether it is possible to measure dry residue and hardness of water enriched by different methods by means of unified coefficients of mineralization, we calculated not only the mean group coefficients of mineralization for each individual enrichment method (K_1 and K'_1), but mean coefficients of mineralization (K_2 and K'_2) for the groups of hard granulated materials (dolomite, dolomite + villiaumite, MP-16 MPU-6, MPU-5), multicomponent salt solutions (K_3, K'_3) differing in water hardness (from 0.48 to 8.0 mg-eq/ℓ) and for all tested methods of enrichment (K_4, K'_4) as a whole. Using these group coefficients of mineralization, we determined the values of dry residue and hardness:

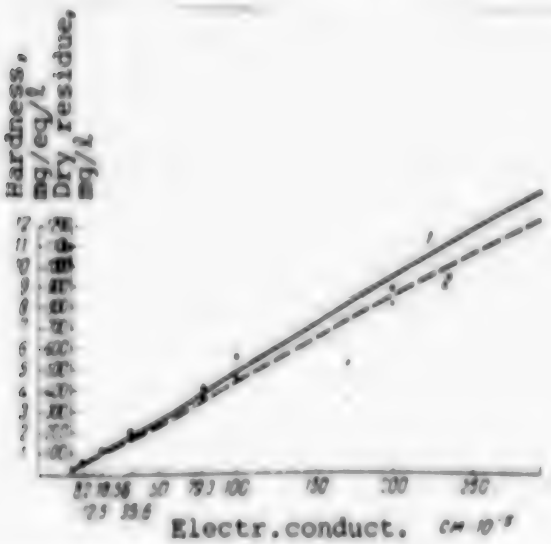
$$\left(K_2 = \frac{X_m}{M_m} \cdot 10^{-3};\ K'_2 = \frac{X_m}{H_m} \cdot 10^{-3}\right)$$

and we determined relative error of measurement, as compared to the results of conventional analytical methods.

Results and Discussion.

The data we obtained are summarized in the Table and graph (see Figure). According to the submitted data, hardness and dry residue of water enriched by different methods constituted 0.32 to 8.0 mg-eq/ℓ and 14.04 to 873.4 mg/ℓ, respectively, when measured by conventional analytical methods. With increase in hardness and dry residue, there was a corresponding increase in electric conductivity, which constituted $2.74 \cdot 10^{-5}$ to $189 \cdot 10^{-5}$ Cm/cm in different samples.

From the data obtained in the experiments with salt solutions and illustrated on the graph (see Figure), we see that there is a linear relationship between hardness, dry residue and electric conductivity.



Electric conductivity of water as a function of dry residue (1) and hardness (2).

According to the data listed in the Table, the group coefficients of mineralization were in the ranges of $K_1 = 0.120\text{-}0.209 \cdot 10^{-5}$ for dry residue and $K_1' = 8.9\text{-}24.0 \cdot 10^{-5}$ for hardness, depending on the method used to enrich water. $K_2 = 0.81 \cdot 10^{-5}$ for dry residue and $K_2' = 10.52 \cdot 10^{-5}$ for hardness in the group of solid minerals; $K_3 = 0.177 \cdot 10^{-5}$ and $K_3' = 20.70 \cdot 10^{-5}$, respectively for the group of salt solutions, $K_4 = 0.179 \cdot 10^{-5}$ and $K_4' = 15.61 \cdot 10^{-5}$ for all tested enrichment methods. Our studies revealed (see Table) that the estimated dry residue and hardness based on group coefficients of mineralization inherent in each separate method of enriching water (K_1, K_1') were close to the experimental data, ranging from 13.1 to 945.0 mg/ℓ and from 0.31 to 8.0 mg-eq/ℓ, respectively. The percentage of relative measurement error was low (0-8.4 for dry residue and 0-4.6 for hardness), and it depended on the method used to enrich water. However, with the use of mean coefficients of mineralization inherent in a set of several enrichment methods (K_2-K_2'; K_3-K_3'; K_4-K_4'), the percentage of relative errors of estimated dry residue and hardness of water increased, constituting 1.2-42.7 and 1.0-121 [sic] (for the group of hard minerals), 0-45.5 and 1.0-13.4 (for salt solutions), 1.3-43.3 and 8.3-43.8 (for all methods of enrichment together).

Thus, these findings indicate that there is a complex correlation between electric conductivity, dry residue and hardness of water, which depends not only on the quantitative, but qualitative salt composition of water, which affects the individual group differences between mean coefficients of mineralization inherent in various methods of salt enrichment. The results we obtained indicate that one can calculate, with a rather high degree of accuracy, dry residue and hardness of enriched recycled water by using the group coefficients inherent in each enrichment method with the following formulas:

$$M = K \cdot X \text{ and } H = K_1 \cdot X$$

where M is the dry residue (in mg/ℓ), H is hardness (mg-eq/ℓ), X is specific electric conductivity (Cm/cm), K is the coefficient of mineralization for dry residue [Cm/(cm•mg)] and K_1 is the coefficient of mineralization for hardness [Cm•ℓ/(cm•mg-eq)]. On the basis of our studies, it was established that one can use the conductometric method for evaluating the quality of water regenerated from the condensate of atmospheric moisture, as it applies to space flight factors, according to dry residue and hardness.

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METHOD FOR SPECTRAL ANALYSIS OF EXTENSIVE TRACINGS OF PHYSIOLOGICAL PROCESSES

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[Article by I. G. Nidekker, submitted 14 Apr 80]

[Text] There are many publications dealing with spectral analysis of cardiac rhythm [1-3]; however, the lack of a standard method for determining spectral density makes it impossible to compare results obtained by different authors. We describe here a method for spectral analysis of lengthy tracings of physiological curves, which has been used for several years and can serve as the basis for devising a standard method of detecting latent periodicity of any physiological process recorded as a function of time. However, before we discuss the principles upon which spectral analysis of physiological processes is based, we must deal with the question of dimensionality of periodic components of heart rhythm. The usual procedure for calculating the function of spectral density yields a curve, from the maximums of which one can determine whether a given periodicity is present. The dimensionality of these periods will be expressed in seconds only if the process being analyzed is a function of time. When interpreting the spectrum of cardiac rhythm, the base information (dynamic series of R-R intervals) is viewed as a function of time in several studies. However, the R-R intervals of the EKG are a function of sequential number of the cardiac cycle (CC), which itself is on a "second" scale [dimensionality]. If this is not taken into consideration, the estimate of periods inherent in a given series of R-R intervals may be incorrect. We can illustrate the possibility of error on the example of plotting an autocorrelation function (ACF). The ACF and spectral density describe the process to the same extent, and the choice of either in each specific instance depends on physical considerations, most often the ultimate purpose of analysis [3]. ACF was constructed for a series of 100 values of R-R intervals. The first 14 values are:

R-R (in s)	0.6	0.65	0.7	0.75	0.8	0.85	0.9	
CC (No)	1	2	3	4	5	6	7	
0.85	0.8	0.75	0.7	0.65	0.6	0.65	etc.	
8	9	10	11	12	13	14		

The AFC of this series, which is illustrated in Figure 1, shows that there is a period of 12 CC, i.e., that the R-R intervals are repeated every 12 CC. In works dealing with spectral analysis of cardiac rhythm, one occasionally encounters the statement that, in such cases, the period equals 12 s. However, the true period in this situation equals $12 \cdot R\text{-}R_m = 9$ s [m = mean]. In the case of

spectral density, one can also make a simple extrapolation so that the scale of the period would also be expressed in seconds, but in any case one should bear in mind that in spectral analysis of a series of R-R intervals, on the spectrum plot we shall have f = (number of CC)$^{-1}$ on the x-axis, rather than $f = s^{-1}$. It is only with a heart rate (HR) of 60/min (R-R$_m$ = 1 s) that the number of CC corresponds to the value of the period expressed in seconds. If, however, HR is 120/min (R-R = 0.5 s), the value of the period expressed by "number of CC" will be double the period expressed in seconds.

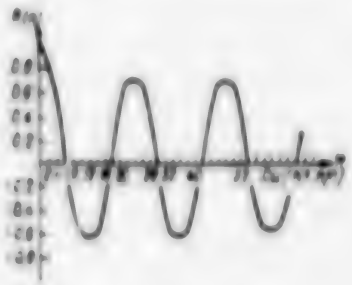

Figure 1.
Autocorrelation function of dynamic series of R-R intervals of the EKG, the start of which is described in the text

The most logical way to correct this error is to convert the base information to a function that is dependent on time. In our studies pertaining to analysis of heart rhythm, we converted the values of R-R intervals into number of CC in time Δt (with Δt = 60 s we obtained the HR). The above series of R-R intervals converted to $SS/\Delta t$ with Δt = 1 s, appears as follows:

CC per second		1.6	1.47	1.2	1.21	1.13
Time, s		1	2	3	4	5
1.16	1.25	1.37	1.5	1.6	etc.	
6	7	8	9	10		

On the plot of this series, we immediately find a wave with a period of 9 s, which coincides with the values of 12 R-R$_m$. Thus, the base information is a function of time; on the x-axis of ACF will be the time, and on the spectral graph $f = s^{-1}$. Since we are dealing with development of a standardized method of spectral analysis of the heart rate, we can state that we are not taking the immediate value of HR in each second, but relating to the time scale, the start of which coincides with the first R wave of the illustrated tracing, i.e., in the above series.

$$1.6\ \text{CC/s} = \left(1 \div \frac{0.4}{0.65}\right)\ \text{CC/s};$$

$$1.47\ \text{CC/s} = \left(\frac{0.25}{0.65} \div 1 \div \frac{0.05}{0.75}\right)\ \text{CC/s, etc.}$$

This method of expressing heart rhythm is convenient for both medical interpretation, since the concept of "pulse" is more familiar to the physician than "series of R-R intervals," and for compressing information: by increasing the value of Δt we can detect slower waves having the same volume of computer memory.

Apparently, a mistake in choice of scale, leading to inaccurate interpretation of the spectrum, is subjective and easy to correct. Another reason for discrepancies in interpreting the results of spectral analysis is related to the nature of the physiological process, and it consists of the fact that it is substantially unstationary. Even with a meticulous experimental set-up, the researcher cannot be entirely certain that the small segment of a physiological process that he is analyzing is indeed a stationary segment, rather than part of a transient process (emotional outbursts, overregulation, etc.). Increasing the length of the tracing

of a physiological process is related to the danger of including various transient and nonstationary segments, i.e., of obtaining a generally nonstationary process.

The opinion is held that the longer the analyzed process, the more accurate the results of spectral analysis. However, the choice of length of a record involves the question of stability of spectrum estimates, which increases with increase in N (number of values in the analyzed series) only in the case of stationary processes. Consequently, it is best to begin spectral analysis of a physiological process on small segments thereof. EKG tracings of 1.5-2-min lengths are sufficient for demonstration of respiratory and 10-30-s components of the spectrum of cardiac rhythm. There are authors [4-5] who also believe that 100-120 R-R intervals are the minimum series, during which the process under study retains some homogeneity.

Figure 2 illustrates spectral density calculated for an 80-s segment of a 5-min tracing of R-R intervals. This record was made with the subject completely calm in seated position. We distinctly see a T wave of 10 s and respiratory wave T = 3 s.* Figure 3 illustrates the spectrum obtained for a segment of this tracing 3 min in length. The 10-s wave has become very diffuse. Thus, with increase in analyzed length of a segment, interpretation of the spectrum became more difficult.

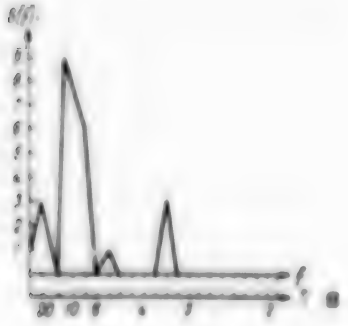

Figure 2.
Spectral density of stationary 80-s segment of 5-min experiment

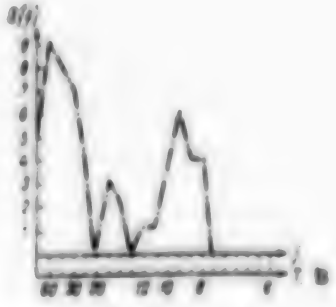

Figure 3.
Spectral density of nonstationary 3-min segment

The method for spectral analysis of extensive tracings of physiological processes used in our studies consists of the following: We assume that a lengthy tracing consists of quasistationary segments, over which transient processes may be superimposed. Quasistationary state of a random process means that its probabilistic characteristics do not change in time. Probabilistic characteristics usually refers to different orders of factors (including correlation function). Since spectral and correlation functions are Fourier conversions from one to the other, invariance in time of one leads to the same in the other. We calculate the spectral density in a quasistationary segment of the process under study. Then this segment "slides" over the entire tracing of the process, and at first its beginning coincides with the start of the record. The length of this segment (T_q) is substantially smaller than the length of the entire record, and it is chosen in time on the basis of certain empirical considerations (for cardiac rhythm this is a

*From here on, we give the spectral densities obtained for a series of R-R intervals that was first converted into pulse, with $\Delta t = 1$ s.

series of 100-120 R-R intervals, for an EEG this refers to runs that depend on the sought rhythm). First, we obtain the value of spectral density $S(f, T_0)$, where T_0 is the time of the start of the tracing. We then move to the right (along the analyzed tracing) over a specified interval τ and again calculate the spectral density over a segment that is T_q in length: $S(fT_0+\tau)$, and so on until the end of our sliding quasistationary segment coincides with the end of the analyzed tracing. As a result of this procedure, we obtain a three-dimensional expression, where the frequency scale of the quasistationary segment is plotted on the x-axis, time corresponding to changes in the process tracing are plotted on the y-axis and values of spectral density are plotted on the z-axis (Figure 4). Such analysis of long tracings of physiological curves yields a detailed picture of changes in frequency structure of a process in the interval analyzed. We see quasistationary segments (one of them is illustrated in Figure 2) and segments with transient processes. If the process is quasistationary over the entire interval of the tracing and has a wave that is slower than $T_q/2$, all of the lines of the dynamic spectrum will resemble one another, while maximum spectral density will be at 0 frequency. In this case, we can go on to detection of slower waves. If the process is substantially unstable over the entire length of a tracing (see Figure 4), the search for a slower wave will yield incorrect results. The process whose spectrum is illustrated in Figure 4 is stationary in pieces. Figure 4 shows that there are segments in the dynamic spectrum of a lengthy tracing (resting) where there is a significant decrease in amplitude of the 8-10-s wave. Respiratory waves (T_r = 3 s) are just as variable. Consequently, one cannot assess the periodicity of physiological processes in a randomly taken short segment thereof, since one could hit on a segment of altered rhythm or a transient process.

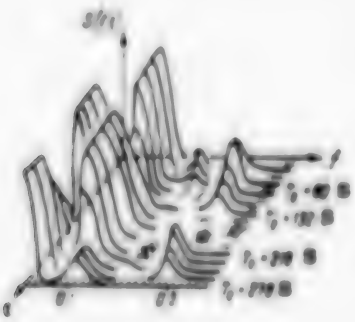

Figure 4.
Dynamic spectrum of 5-min tracing of R-R intervals with an 80-s segment of quasistability

Presentation of the dynamic spectrum in the form of a graph (see Figure 4) is inconvenient, both from the standpoint of plotting it and interpretation. A computer printout in digital form is more convenient for these purposes. A printout of digital values of the spectrum, for which Figure 1 was plotted, is illustrated in the Table. The numbers in the lines of this table corresponding to standardized (for the highest number in a horizontal line) values of spectral density. The first, top line refers to periods (or frequencies) that can be encountered in the selected quasistationary segment. The first column on the left is real time (T_0, start of record), τ = 3 s. The second and third columns refer to mean and standard deviations of CC values, respectively, per second in quasistationary segments. They serve to assess the stability of the process under study. On the example of the respiratory components of the spectrum of cardiac rhythm, we see that we cannot narrow down the peak of the spectrum to the respiratory rate, not because we used an imperfect filter, but because of irregularity of breathing itself, i.e., we cannot state that the respiratory rate equals 0.2 Hz, we should say: "in the range of 0.16-0.32 Hz." The peak of the spectrum for respiratory rate is also

in this range. For this reason, in our opinion, one should not get carried away with the choice of optimum filter for estimating spectral density when conducting spectral analysis of physiological processes.

Dynamic spectrum of 3-min tracing of R-R intervals with 80-s quasistationary segment

Time, s	CC/σ*	σ	Period, s													
			40	30	15	10	8	6	5	5	4	4	3	3	3	2
$T_q - 3$	1.584	0.073	2	4	1	9	6	0	1	0	0	0	0	0	0	0
	1.585	0.082	0	3	1	9	4	0	1	0	0	0	0	0	0	0
	1.583	0.076	0	1	0	9	4	0	0	0	0	0	0	0	0	0
	1.589	0.074	0	1	0	9	4	0	0	0	0	0	0	0	0	0
	1.597	0.078	0	2	0	9	4	0	1	0	0	0	0	0	0	0
	1.613	0.086	0	3	0	9	6	0	1	0	0	0	0	0	0	0
	1.624	0.090	1	2	0	9	7	0	1	0	0	0	0	1	0	0
	1.626	0.092	2	3	0	9	7	0	1	0	0	0	0	1	0	0
	1.627	0.095	1	3	0	9	6	0	1	0	0	0	0	1	0	0
	1.639	0.091	2	4	0	9	5	0	1	0	0	0	0	2	0	0
$T_q - 60$	1.653	0.093	5	3	0	9	4	0	0	0	0	0	0	3	0	0
	1.664	0.097	5	4	0	9	6	0	1	0	1	0	0	4	0	0
	1.671	0.093	9	5	2	7	6	0	0	0	0	0	0	5	0	0
	1.675	0.088	9	3	1	4	5	0	0	0	0	0	0	3	0	0
	1.676	0.085	9	4	1	3	4	0	0	0	0	0	0	2	0	0
	1.678	0.082	9	6	2	4	3	0	0	0	0	0	0	2	0	0
	1.685	0.082	9	7	4	6	2	1	0	0	0	0	0	1	0	0
	1.687	0.082	9	6	3	6	2	1	0	0	0	0	0	1	0	0
	1.683	0.080	9	7	6	6	3	2	0	0	0	0	0	1	0	0
	1.679	0.079	9	5	6	6	2	2	0	0	0	0	0	0	0	0
	1.679	0.074	9	5	4	7	3	3	0	0	0	0	0	0	0	0
	1.691	0.068	6	7	3	9	4	4	0	0	0	0	0	0	0	0
$T_q - 132$	1.690	0.069	8	8	2	9	4	4	0	0	0	0	0	0	0	0
	1.679	0.085	3	9	1	7	6	4	0	0	0	0	0	0	0	0
	1.670	0.084	2	8	2	9	5	2	0	0	0	0	0	0	0	0
	1.664	0.081	3	5	1	9	5	1	0	0	0	0	0	0	0	0
	1.668	0.081	3	4	0	9	4	1	0	0	0	0	0	0	0	0
	1.669	0.079	3	5	0	9	5	0	0	0	0	0	0	0	0	0
	1.673	0.078	3	5	0	9	6	0	0	0	0	0	0	0	0	0
	1.676	0.075	4	5	0	9	5	0	0	0	0	0	0	0	0	0
	1.675	0.074	4	5	0	9	5	0	0	0	0	0	0	0	0	0
	1.675	0.074	3	6	0	9	6	0	0	0	0	0	0	0	0	0
	1.674	0.074	3	6	0	9	6	0	0	0	0	0	0	0	0	0
	1.670	0.076	5	6	0	9	7	0	0	0	0	0	0	0	0	0
	1.667	0.075	6	6	1	9	8	1	0	0	0	0	0	1	0	0
	1.668	0.078	4	5	2	9	5	0	0	0	0	0	0	1	0	0
$T_q - 216$	1.672	0.072	9	4	0	5	6	1	1	1	0	0	0	2	0	0
	1.692	0.071	9	1	1	2	2	0	0	0	0	0	0	3	0	0
	1.705	0.072	9	0	0	1	2	0	0	0	0	0	0	4	0	0
	1.713	0.078	9	0	1	0	3	0	0	0	0	0	0	4	0	0
	1.723	0.079	9	0	1	0	3	1	0	0	0	0	0	3	0	0
	1.726	0.079	9	0	1	1	4	0	0	0	0	0	0	2	0	0
	1.733	0.082	9	0	0	1	4	0	0	0	0	0	0	1	0	0
	1.748	0.085	9	0	0	1	3	0	0	0	0	0	0	0	0	0
	1.754	0.084	9	0	0	1	2	0	0	0	0	0	0	0	0	0
	1.764	0.080	9	0	0	1	2	0	0	0	0	0	0	0	0	0
	1.772	0.073	9	0	2	2	3	2	0	0	0	0	0	0	0	0
	1.781	0.059	9	2	1	6	8	4	0	0	0	0	0	0	0	0
	1.790	0.052	6	2	6	7	9	8	0	1	0	1	0	0	0	0
	1.797	0.051	8	2	4	6	9	7	0	2	0	0	0	1	0	0
	1.786	0.050	4	5	2	7	9	2	1	0	1	0	0	1	0	0

*Mean pulse in studied segment T_q.

Thus, the method of spectral analysis of physiological processes we have described here permits evaluation of frequency structure thereof in segments that are quasi-stationary and variable over the length of the entire tracing of the process (i.e., determination of stationary segments and segments where the process changes). With this method, there is no need to wait for a physiologically stable state to start recording any physiological curve. One can determine when the transient process stops and a stationary segment begins from the appearance of the dynamic spectrum. In dynamic spectra obtained for 20-30-min tracings of R-R intervals, a change from one wave to another occurred several times in the recording (the respiratory waves are particularly labile). Perhaps, the time of change from one rhythm to another will be informative in evaluating the state of the organism. If the graph of the dynamic spectrum is indicative of stability of the process under study, by increasing Δt for R-R intervals we can move on to evaluation of slower waves.

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BRIEF REPORTS

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USE OF NOSPANUM IN COMBINATION WITH CERTAIN VITAMINS AGAINST SEASICKNESS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 82-83

[Article by V. V. Usachev, V. V. Sabayev, A. D. Matveyev and A. G. Popov, submitted 14 Apr 80]

[Text] The search for effective drugs against seasickness constitutes an important part of space medicine, since a considerable number of cosmonauts developed vestibulovegetative disorders at the early stages of orbital flight [1-3]. In this respect, specialists have been drawn to no-spa* (Nospanum), whose action is similar to that of papaverine [4, 5] and which has marked and prolonged spasmolytic activity. This effect is attributable to the direct influence of no-spa on smooth muscles of vessels and some organs, in particular those of the abdominal cavity, kidneys and lungs [6]. According to previously published data [7-9], the tonus of peripheral vessels increases with cumulative vestibular stimuli. On the basis of the foregoing, we decided to test the efficacy of this product against seasickness, when combined with certain vitamins.

Methods

We used three drug combinations proposed by Hungarian researchers. The first product consisted of a combination of no-spa (50 mg), vitamins B_1 (100 mg) and B_6 (50 mg), and lactose; the second contained no-spa combined with vitamins B_6 (50 mg), E (2.5 mg) and lactose (150 mg); the third consisted only of vitamins B_1, B_6 and lactose. Scopolamine in a dosage of 1 mg was used as the standard product.

The tests were conducted with an electric VU-4m revolving unit equipped for recording the main parameters of central hemodynamics (arterial pressure, heart rate, rate of propagation of pulse wave over elastic vessels, period of ejection of blood from the left ventricle and others). We calculated stroke and minute volumes according to Bremser-Ranke in the modification of N. N. Savitskiy [10], and we determined peripheral resistance using the formula of Poiseuille [11].

Seasickness was simulated by exposing man to accelerations by the system of I. I. Bryanov [12]. The subject was rotated until marked autonomic reactions, appeared, grades II-III in the classification of K. L. Khilov and G. G. Kulikovskiy [13, 14]. Physiological functions were recorded before (3-5 min prior to) and after (after 2-3 min) each test. In all, there were 14 subjects used in 7 series,

*Translator's note: No-spa is manufactured in Hungary.

with a total of 91 tests. We adhered to the principles of a double-blind control in conducting the tests. The products were handed out to the subjects in a different room 2 h before submitting them to accelerations. The obtained data were submitted to statistical processing with the use of Student's criterion and, in some cases, sign criterion [15].

Results and Discussion

The results of our studies are listed in the Table.

Endurance of low levels of accelerations after intake of drug products

Series	Number of subjects	Endurance, min
Control 1	14	3.8±0.3
Scopolamine	13	4.3±0.7
Placebo (lactose)	14	4.2±0.7
No-spa + vitamin B_1 + vitamin B_6	14	2.9±0.3*
No-spa + vitamin B_6 + vitamin E	12	3.8±0.4
Vitamin B_1 + vitamin B_6	12	3.7±0.5
Control 2	12	3.8±0.4

*$P<0.05$, as compared to control 1.

Our studies failed to demonstrate a positive effect of the three products tested on endurance of low levels of complex accelerations. In the case of using no-spa combined with vitamins B_1 and B_6, the effect was reliably negative ($P<0.05$). The similar results obtained in determining tolerance of the first and subsequent low levels of accelerations (see Table, control 1 and control 2) serve as grounds to rule out the effect of repetition of vestibular stimuli. In our tests, there was enhancement of vestibulovegetative stability (VVS) after intake of scopolamine; however, even in this case, the changes in VVS level were unreliable because of the wide scatter of data.

The results of analysis of clinical findings were confirmed in the data referable to physiological functions. In the control series, in the immediate aftereffect period, we observed elevation of diastolic and drop of systolic arterial pressure, and the pulse amplitude usually declined, which was associated with some decrease in systolic blood volume. The direction of changes in arterial pressure and stroke volume was analogous with intake of the drugs. It should be noted that with intake of vitamins B_1 and B_6 the hemodynamic changes associated with vestibular stimuli were minimal.

Thus, as shown by the results of our studies, we failed to demonstrate a positive effect of spasmolytics on level of VVS. It has been demonstrated in several works [16, 17] that there is a decrease in tonus of intracranial vessels with development of the heaving-vomiting reflex during rotation. In such cases, administration of spasmolytics could aggravate decompensation of cerebral circulation, and perhaps this was the chief cause of diminished VVS with intake of no-spa.

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FLIGHT-RELATED CHANGES IN PARAMETERS OF EXTERNAL RESPIRATION IN HELICOPTER CREWS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 83-84

[Article by Yu. N. Kamenskiy, submitted 10 Mar 80]

[Text] Investigation of physiological mechanisms of fatigue plays a part in the study and evaluation of pilot efficiency [1]. Our objective here was to examine functional changes in the external respiratory system of helicopter crews in the civil aviation that were related to flights.

Methods

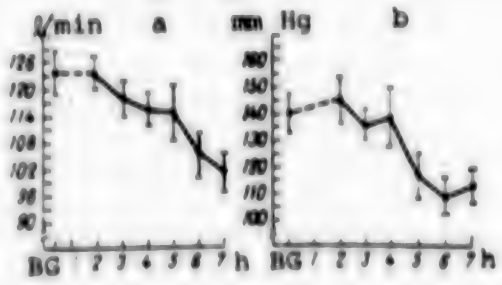
We examined 86 crew members of cargo helicopters who participated in usual work flights. All of the subjects were divided into six groups according to flying time per shift (2, 3, 4, 5, 6 and 7 h). The groups were standardized according to job title and age. Subjective evaluation of fatigue was studied by means of anonymous questionnaires filled out by crew members. We determined vital lung capacity (VC), the pneumotonometric index (PTI) according to Kh. A. Izakson [2] and maximum breathing capacity (MBC) before and after the flights.

Results and Discussion

We demonstrated the dynamics of postflight changes in MBC and PTI as a function of flying time. VC showed virtually no postflight change, which is consistent with the data of V. I. Kopanev et al. [3]. A 4.9 and 4.7% decrease in MBC and PTI, respectively, was noted after a work load of 3 h per shift (see Figure). These parameters changed the most after 5 and 4 h of flying: 12.0% decrease in MBC and 12.1% decrease in PTI ($P<0.05$). These changes coincided with the time of appearance of subjective signs of fatigue and preceded build-up of the latter. A tired feeling appeared after a work load of 5 h per shift in 42.9% of the subjects, after 6 h in 86.7% and after 7 h in 85.7%. There was an analogous increase in number of cases of negative attitude toward continuing with the flights (35.7, 66.7 and 78.6%).

It is known that the external respiratory system reacts rather sensitively to development of generalized fatigue under the influence of various factors [3, 4]. The decline of MBC and PTI in crew members in the course of a flight shift was

indicative of diminished functional reserves of the system of external respiration and body as whole, which was apparently related to development of fatigue. Noise and vibration, with predominant significance of the latter [5], played a rather substantial role in development of fatigue in helicopter pilots. Vibration can have a direct effect on external respiration by impairing the mechanical properties of lung tissue. It is known that the mechanical stability of the alveoli depends on surfactant properties of fluid covering their internal walls [6]. Under the influence of vibration, the surfactant properties of biological fluids change [7], and this may be associated with impairment of mechanical stability of the alveoli, collapse thereof and, consequently, deterioration of bronchial patency, diminished functional respiratory reserve and, in particular, MBC.



Dynamics of MBC (a) and PTI (b) in helicopter crews in the course of a work shift. X-axis, flying time; y-axis, absolute values of parameters; BG--background

The changes in PTI are mostly related to development of general fatigue, since this parameter depends on the strengh of respiratory muscles and is correlated with the strength of other muscles of the body [8]. If fitness [efficiency] of flight personnel is interpreted as potential capabilities of functional systems [9], one can assess the pilot's reserve capacities as a whole, as well as degree of his fatigue according to the dynamics of PTI.

Consequently, when flying in helicopters, the crew presents a decrease in functional reserves of external respiration during the flight shift, which is the result of the direct effect of vibration on this system and development of general fatigue. The most marked decline of respiratory reserve is observed after 5-6 h of flight work, when subjective signs of fatigue appear and build up. This suggests that the functional changes in the system of external respiration, evaluated according to MBC and PTI, may be used to detect fatigue in flight personnel.

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CHANGES IN BIOELECTRICAL ACTIVITY OF THE MYOCARDIUM OF FLIGHT PERSONNEL UNDER THE INFLUENCE OF THEIR WORK LOAD

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 84-85

[Article by V. D. Vlasov, Yu. D. Karnaukhov and O. P. Dmitriyev, submitted 22 Apr 80]

[Text] The functional capacities of man diminish with age [1-7], and this affects the quality of professional performance. The literature does not shed enough light on the question of functional capacities of flight personnel as related to age. It is important to know the age-related distinctions of pilot reactions to flight factors for prevention of flight incidents and to solve problems of expertise.

Studies of the functional state of the cardiovascular system, which largely determines the pilot's reaction to flights, have special importance [8-10].

Methods

We examined 72 crew members of AN-22 aircraft, 18 to 45 years of age, in the period of preflight training (background), 1-3 h after flights, the morning (12 h after flight) and 24 h after flight using electrocardiography (EKG) and quantitative, spatial vectorcardiography (VEKG) according to Yu. N. Shishmarev [11]. All of the flights were at low altitude and lasted about 3 h. The pilots were divided into 3 age groups, with 24 people in each: 1st group--18-25 years old, 2d group--26-35 years and 3d--36-45 years. To eliminate the effect of specific flight work on the results of the study we used the same number of various specialists in each group--6 commanders, 6 copilots, and 3 of each of the following: navigators, radio operators, flight engineers [or mechanics] and gunners.

We examined the medical records of this personnel and performed a physical that corresponded to the scope of the medical flight commission. All crew members were deemed to be in good health and fit for flight work.

A Physiograph-066 instrument was used to record the EKG and VEKG. With the VEKG we studied 10 parameters characterizing the magnitude and direction of cardiac DS [electromotive force?] in phases of depolarization and repolarization of the ventricles. We calculated the magnitude and ratio of integral vectors of QRS and T, direction of these vectors in the frontal and horizontal planes, angle between QRS and T vectors in these planes and in space.

Results and Discussion

There was a statistically reliable increase in duration of P wave in flight personnel 36-45 years of age, 1-3 h after flight, as compared to the preflight period ($P<0.05$). These changes indicated that the slowing of intraatrial conduction was probably due to an increased load on the atria. We failed to demonstrate reliable changes in other EKG parameters in the postflight period.

The VEKG revealed a statistically reliable increase in angle between QRS and T vectors in space only in the older age group for the first 3 h after flight. The changes in all other VEKG parameters after flight were insignificant in all age groups.

The size of the spatial angle between QRS and T is an important indicator characterizing the ratio between depolarization and repolarization processes. Increase thereof is indicative of an increase in discordance of the T vector in relation to the QRS vector [12, 13].

The demonstrated postflight changes in EKG and VEKG parameters did not exceed the range of the conventional norms and were of no pathological significance. However, they were indicative of some decline of adaptive capabilities of the myocardium with age with regard to flight factors, apparently attributable to the distinctive features of myocardial metabolism.

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EFFECT OF SOFT DIET ON THE PROCESS OF FORMATION OF ENTERIC CONTENTS DURING NATURAL DIGESTION

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 85-87

[Article by M. I. Bryuzgina, T. S. Popova, V. I. Lebedev and Yu. M. Gal'perin, submitted 18 Oct 79]

[Text] Works of recent years have shown that the composition of chyme at the exit from the gastroduodenal system is important to assimilation of nutrients [1, 2]. Our objective here was to examine the question of the extent to which replacement of usual intake of food by mouth with the use of natural products by fistular injection into the stomach of a standard soft [gruel-like] diet [3] influences chyme formation in the gastroduodenal system and absorption of some ingredients in the small intestine.

Method

Experiments were conducted on preoperated mongrel dogs weighing 20-25 kg, in whom we implanted 5 fistulae: 1 in the stomach, 1 in the duodenum and 3 in the small intestine. Segments of the intestine between the second and third, as well as between the fourth and fifth fistulae were brought out into a skin flap in the form of a "suitcase handle." After ligating the bridges of the fistulae located above and below them, we connected them in an external anastomosis, into which we inserted the main sensory of an RKE-2 magnetic flowmeter. This enabled us to record in the course of the experiment the volume of chyme passing from the gastroduodenal region into the small intestine and, at the same time, to measure the volume of chyme passing out of the temporarily isolated 50-cm segment of small intestine. After connecting the recording devices, in the main series of experiments we injected into the stomach 555 g of gruel containing 65.2 g protein, 42.0 g fat and 153.0 g carbohydrates. There was approximately the same amount of the main nutrients in the diet of natural products given to dogs in control experiments.

The experiment was stopped after the stomach was completely empty, as checked by opening the gastric fistula. We assayed sodium, potassium, calcium, magnesium (with a flame photometer), total and nonprotein nitrogen according to Kjeldahl in chyme samples passing from the gastroduodenal system and distal part of the small intestine. The experimental results were submitted to statistical processing with the use of Student's criterion.

Results and Discussion

Table 1 lists information about the concentrations of the tested ingredients entering the stomach after intake of the usual and gruel diet, as well as changes in these concentrations in the duodenum and distal small intestine over a 6-h period of digestion.

Table 1. Concentration of tested ingredients of chyme M±σ (n = 60)

Constituent	Usual diet			Soft diet		
	stomach	duodenal chyme	chyme of small intestine	stomach	duodenal chyme	chyme of small intestine
Fluid, g%	75	93±2	93±2	77	90±5	95±3
Sodium, mg%	92	131±26	174±20	175	164±12*	197±17*
Potassium, mg%	183	57±9	62±11	130	45±3*	45±3*
Calcium, mg%	79	46±8	67±18	45	29±11*	48±13
Magnesium, mg%	18.8	8±1	12±2	8.8	7±1	13±1
Total nitrogen, mg%	1165	380±93	440±85	886	516±182	534±80

*Reliable differences, as compared to the ordinary diet.

The insignificant decrease in sodium concentration with the use of the soft diet and increase with intake of normal diet are indicative of passage of endogenous sodium into the enteric system. At the same time, there was a correlation between concentrations of ingredients of duodenal chyme and the chyme extracted from the distal small intestine, on the one hand, and levels of the tested components in the consumed food.

The data listed in Table 1 also indicate that the composition of chyme in the distal segment of the intestine continued to be stable, and we demonstrated the same tendency of changes for both tested diets.

The increase in sodium, total and nonprotein nitrogen, which was observed with the ordinary diet, was not inherent in the soft diet (Table 2).

The changes in the chymus with the soft diet were manifested only after they passed through the initial segment of the small intestine. In spite of the lower calcium and total nitrogen content of the soft diet, the concentration parameters of chyme of the small intestine were found to be considerably higher than with intake of the usual diet, which could be attributed to the relatively rapid absorption of fluid in the initial segment of the small intestine.

The results of the experiments revealed that there was no change in general pattern of chyme production with the use of the soft diet. At the same time, there were some specific distinctions of chyme production with intragastric administration of the gruel diet, and they were better demonstrable in hourly analysis of changes; in the first place, there was no increase in concentration of sodium and total nitrogen between the first and sixth hours of active digestion; in the second place, there was gradual and substantial decrease in calcium concentration, and in the third place, with the soft diet the concentration of total nitrogen in duodenal chyme was substantially higher during the first hours of digestion than with the usual diet.

Table 2. Concentrations of tested constituents of chyme in the course of active digestion of soft diet (mg%) (M±σ, n = 10)

Hour	Duodenal chyme							Chyme of small intestine						
	water	K	Na	Ca	Mg	total N	non-protein N	water	K	Na	Ca	Mg	total N	non-protein N
1	95±5	52±11	169±23	38±26	6±2	393±68	150±77	95±2	57±12	168±43	59±17	11±4	539±127	265±129
	(92±2)	(67±19)	(114±38)	(42±15)	(13±6)	(235±63)	(179±66)	(93±3)	(71±16)	(145±46)	(39±22)	(9±3)	(256±112)	(169±59)
2	95±4	52±12	162±40	78±19	7±1	406±168	189±120	94±1	49±8	193±50	60±46	11±5	514±154	238±123
	(93±3)	(60±23)	(103±45)	(46±22)	(6±2)	(343±108)	(186±63)	(92±2)	(65±18)	(121±32)	(63±17)	(11±2)	(311±84)	(166±69)
3	96±4	50±10	159±32	38±26	12±9	378±141	236±127	96±3	46±8	180±27	55±40	14±3	464±201	313±141
	(94±2)	(62±16)	(136±39)	(49±21)	(9±2)	(414±261)	(231±56)	(92±2)	(64±28)	(154±58)	(90±77)	(14±7)	(535±136)	(171±80)
4	94±3	36±3	151±27	36±25	7±1	496±133	293±93	95±4	37±9	198±48	44±30	44±6	576±214	378±76
	(93±3)	(54±11)	(127±35)	(44±12)	(7±2)	(336±209)	(201±96)	(93±2)	(57±18)	(172±59)	(52±38)	(14±7)	(398±175)	(229±63)
5	95±2	44±11	204±31	29±19	6±1	317±79	176±70	94±2	79±4	199±15	35±25	12±1	445±199	230±41
	(94±2)	(47±15)	(136±41)	(58±47)	(7±3)	(495±185)	(304±58)	(92±3)	(60±17)	(208±57)	(87±66)	(14±8)	(554±247)	(281±61)
6	96±3	35±3	140±2	7±1	5±1	347±151	169±75	96±4	63±7	241±6	36±14	12±1	671±51	190±22
	(92±2)	(50±17)	(167±54)	(38±20)	(7±3)	(459±282)	(313±89)	(93±2)	(52±19)	(246±63)	(71±23)	(12±4)	(587±260)	(346±154)

Note: Data referable to the usual diet are given in parentheses. H_2O is shown in g%.

On the whole, the obtained data are indicative of the fact that, in the case of fistular feeding of a soft diet, while there is retention of the general tendency of preserving the composition of the enteric contents, formation of chyme presents some distinctions that may affect the rate of digestion and absorption of chyme constitutents at different stages of digestion.

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T AND B LYMPHOCYTES AS RELATED TO ADAPTATION TO HIGH ALTITUDES

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 87-89

[Article by M. I. Kitayev and A. G. Tokhtabayev, submitted 2 Jan 80]

[Text] There is little coverage in the literature of the immunological aspects of man's adaptation to a mountain climate [1]. Yet this is a rather important problem in view of the need to maintain immunological homeostasis under extreme natural conditions with a shortage of oxygen.

Previous studies demonstrated a brief decrease in synthesis of immunoglobulins (Ig) A, M, G and attenuation of blast transformation reaction of lymphocytes with phytohemagglutinin during the first days of adaptation to high altitude [1, 3]. However, these studies were conducted without quantitative assay of T and B lymphocyte populations. Our objective here was to make a complex study of quantity and function of T and B lymphocytes in the course of man's adaptation to high altitude.

Methods

We examined the immunological status of 18 essentially healthy men 20-24 years old, at different stages of adaptation to the Tyan-Shan mountains. We first examined them in the lowlands (760 m above sea level), then when they moved to the mountains (3200 m) on the 3d-5th and 25th-30th days of adaptation. Immunological examination of quality of function of the immune system included a differentiated study of T and B systems of immunity.

We used lymphocytes isolated from peripheral blood in a gradient of ficoll-urotrast to identify and assay T and B cells. T lymphocytes were demonstrated by the method of spontaneous rosette formation with ram erythrocytes [4]. B lymphocytes were demonstrated by their ability to form rosettes with erythrocytes loaded with antibodies and complement [5]. A lymphocyte surrounded by a corona of three or more adherent foreign erythrocytes was considered to be a rosette-forming cell. We recorded absolute (per μl blood) and relative (percentage) quantities of T and B rosette-forming cells. We judged the functional state of T lymphocytes in the lymphocyte blast-transformation reaction (RBTR) with phytohemagglutinin (PHA) and concanavalin A (ConA), and according to spontaneous blast transformation [6]. Functional assessment of B lymphocytes was made according to Ig synthesis by the method of radial immunodiffusion [7].

Results and Discussion

At the early stage of adaptation (3d-5th days), there was a reliable decrease in rosette-forming T cells to 701.0±37.6/μl versus 993.0±65.7 (Table 1), as a reaction to the stress situation. The shortage of T cells was associated with a decline of their potential capacity for blast transformation under the influence of PHA; at this time, the RBTR with PHA constituted 58.68±1.52, versus the base level of 64.62±1.29. All this was indicative of depression of the T system of immunity during the first days in the mountains.

Table 1. T system of immunity in essentially healthy subjects with brief adaptation to altitude hypoxia

Altitude above sea level, m	n	Day of examination	Rosette-forming T cells		PHA stimulated cells, %	ConA stimul. cells, %	Stimulated cells without PHA and ConA, %
			%	absolute quantity/mm³ blood			
760	18	Base data	59.2±2.6	993±65.7	64.62±1.29	56.76±5.38	8.08±0.95
3200	17	3–5	48.2±2.7*	701±37.6*	58.68±1.52*	63.18±5.43	4.16±0.58*
3200	18	25–30	56.0±2.3	1001±79.2	64.82±1.27	58.05±4.88	4.01±0.42*

*P<0.05, here and in Table 2.

Table 2. B system of immunity in essentially healthy subjects with brief adaptation to altitude hypoxia

Altitude above sea level, m	n	Day of examination	Ig sera, IU/ml			Rosette-forming B cells	
			M	G	A	absolute quantity/mm³ blood	%
760	18	Base data	217.7±15.6	168.3±8.6	99.9±6.3	219.0±22.4	13.05±1.06
3200	17	3–5	176.9±13.9*	140.8±6.3*	97.3±5.9	276.0±19.3	18.5±1.1*
3200	18	25–30	386.2±59.7*	159.5±15.0	103.6±7.7	313.0±26.1*	17.7±1.27*

On the subsequent days of adaptation, the absolute quantity and functional activity of these cells were restored, reaching the parameters of the "immunological" normal by the 25th-30th day. The blast transformation reaction with concanavalin A showed virtually no change during brief adaptation to the mountains. In all likelihood, concanavalin stimulates blast transformation of the subpopulations of T cells that manifest resistance to low partial oxygen tension. During the stay in the mountains, there was a decrease in functional activity referable to transformation into juvenile blast forms. Thus, on the 3d-5th day of adaptation, spontaneous transformation constituted 4.16±0.58, on the 25th-30th day it was 4.01±0.42, versus 8.08±0.95 in the lowlands (P<0.05).

It was of some interest to examine the B system of immunity which, as we know, is involved in antibody synthesis. The absolute quantity of rosette-forming B

cells in the systemic circulation increased during adaptation to altitude hypoxia from 219.0±22.4 (lowlands) to 276.0±19.3 on the 3d-5th day and 313.0±26.1 on the 25th-30th day; however, these cells were functionally deficient during the first days of adaptation with regard to antibody production, since we observed a decrease in concentration of IgM and IgG (Table 2). During adaptation, IgG reached the base level, while IgM synthesis increased drastically. Thus, activation of B rosette formation was associated with intensification of IgM synthesis, which reflects, as we know, the early immunological reaction to thymus-dependent antigens, i.e., antibodies of the primary response [8].

The demonstrated phasic changes in immunological reactivity of the body under extreme environmental conditions conformed with data in the literature concerning the dynamics of immunity in the presence of stress [11].

The deficiency of cellular and humoral immunity during the first week of the adaptation period was indicative of depression of functional activity of the immunogenic system. The mechanism of development of immunological deficiency during this period may be related to many factors, primarily the "hypoxic syndrome," which diminishes immunogenesis. In view of the information concerning activation of the adrenals during the first few days of adaptation to high altitude [9, 10], one would think that corticosteroids have an immunosuppressive effect on immunogenetic processes. Such changes are adaptive, and they can be interpreted as a stress reaction.

Thus, the process of man's adaptation to high altitude is characterized by phasic changes in proportion and functional activity of T and B lymphocytes.

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BIOCHEMICAL PARAMETERS OF BLOOD IN PATIENTS WITH FUNCTIONAL DEVIATIONS OF VERTICAL SEMICIRCULAR CANALS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 p 89

[Article by L. N. Kekhayov (People's Republic of Bulgaria), submitted 31 Mar 80]

[Text] This work is a continuation of studies of the effects of vestibular stimulation on biochemical constants of blood. The vertical canals of the labyrinth, which constitute a powerful antigravity vestibular group in weightlessness, together with the otolith system, would undergo functional changes. A clinical and biochemical study was made of 25 patients with altered function of the vertical semicircular canals of the labyrinth (hyporeflexia and hyperreflexia of anterior or posterior canals, or combined change in their function).

Determination was made of potassium, sodium, calcium, phosphorus and chloride levels in blood serum before and 15 min after vestibular stimulation.

Before stimulation, several patients presented a tendency toward increase in sodium and occasionally decline of blood sugar level. Vestibular stimulation elicited changes in different directions in the parameters studied. In a small number of observations of functional groups (2 to 6 people), we observed changes in the endogenous environment of the body in the presence of hyporeflexia and hyperreflexia of the antigravity system of the semicircular canals.

The demonstrated tendencies of changes in biochemical parameters of blood cannot be considered specific for functional disturbances of the vertical canals of the labyrinth. However, this pathology not only elicits hyperextension reactions of the body, sensory and vestibulovegetative disturbances, but affects the biochemical parameters of blood. The use of this clinical model is recommended for research as it applies to problems of space medicine.

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DISCUSSIONS

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SIGNIFICANCE OF VESTIBULAR SYSTEM TROPHICS IN THE MECHANISM OF VESTIBULOVEGETATIVE MANIFESTATIONS OF MOTION SICKNESS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 pp 89-91

[Article* by N. I. Arlashchenko, submitted 26 Jan 79]

[Text] The vestibular stimuli that man encounters in moving systems, in particular during orbital flight in a spacecraft, should be referred to the category of stressors. Any stressor stimuli may be the cause of a marked autonomic reaction with the same manifestations as motion sickness (nausea, vomiting, hyperhidrosis and others). This applies, for example, to the body's general reaction to radiation, intoxication and trauma. This reaction is the result of intensification of afferent impulsation, which occurs with impairment of homeostasis of organs and tissues that are damaged or altered as a result of radiation. In this respect, this reaction should be called adaptive-trophic, and it is directed at maintenance of stability of the endogenous environment, involving the main center of regulation of autonomic functions, the hypothalamus.

In spite of the absence of indications in anatomical works [4, 5] of the existence of innervation of the vestibular system by the trigeminal nerve, we always have the opportunity to become convinced that it exists in observing, for example, the severe nociceptive reaction of animals to surgery on the inner ear. Moreover, trophic changes in the labyrinth have been demonstrated after injury to the trigeminal nerve [6]. Destruction of the trigeminal ganglion of rabbits, which creates a site of prolonged stimulation in the system of the trigeminal nerve [7], led to attenuation of labyrinthine reactions to angular accelerations on the 7th-10th postoperative day [8]. Eye rotation when the animals were inclined, as well as other postural reflexes, diminished, as compared to normal. There was impairment of associative reactions of eye muscles with changes in spatial position of the animals. Morphological examination of the labyrinth revealed trophic disturbances, destruction of receptor structures which developed by this time, dystrophy of secretory epithelium, which is the morphological substrate of the hematolabyrinthine barrier of the vestibular part of the inner ear. Along with the secretory epithelium of the vascular band of the cochlear segment, this epithelium forms endolymph, which is the nutrient medium for inner ear receptors [9, 10].

It was established that destruction of the trigeminal ganglion leads to drastic increase in permeability of the hematoophthalmic barrier to intravenously injected fluorescein [11] and blood protein [12], which normally do not penetrate the vasotissular barrier. As a result of increased permeability of this barrier, there is

*Discussion referable to genesis of vestibulovegetative disorders during space flights [1-3].

significant elevation of intraocular pressure [13]. The mechanism of this disturbance cannot be observed visually, but similarly to the functional role of the hematolabyrinthine barrier with injury to the trigeminal nerve, it apparently consists of analogous destruction of the vasotissular barrier. It is quite probable that this is associated with changes in electrolyte and protein composition of endolymph and perilymph and, consequently, impairment of correlation between osmotic pressure of labyrinthine fluids. Indeed, after destruction of the trigeminal ganglion, we always observed compression of the membranous labyrinth on histological sections of the inner ear, indicative of impairment of correlation between endolymph and perilymph pressure, with prevalence of the latter [8]. Perhaps, the observed degeneration of receptors of the vestibular system and attenuation of specific labyrinthine function due to impairment of intralabyrinthine pressure is a phenomenon of the same order as loss of specific visual function in the presence of glaucoma, which is characterized by elevation of intraocular pressure.

The change in pressure of lymph of the ear can apparently be a powerful stimulus for baroreceptors and other interoceptors contained in the soft tissues of the membranous labyrinth.

The trigeminal nerve is a sensory conductor from receptors of the mucosa of the mouth, nose, ear and conjunctiva, with the exception of those parts that are represented by specific receptors of sense organs, which are innervated by the 1st 2d, 7th, 8th and 9th pairs of cranial nerves [4]. The trigeminal nerve is connected through the reticular formation with the vestibular nuclei and nuclei of the vagus and glossopharyngeal nerves [4]. Consequently, stimulation thereof, like stimulation of the vestibular system, could be associated with autonomic reactions in the form of slow pulse, arterial pressure drop, nausea, vomiting, cooling of hands and feet, facial pallor, appearance of cold sweat and others [14].

Perhaps the displacement of the membranous labyrinth in perilymph due to the unusual gravity factors, or change in endolymph pressure and related deformation of the walls of the membranous labyrinth are a direct stimulus for the endings of the sensory trigeminal nerve. For example, elimination of the pressure of weight of otic lymph upon the lower parts of the endolymphatic sac in weightlessness could lead to intensification of production thereof by the hematolabyrinthine barrier and, consequently, to elevation of intralabyrinthine pressure. It could also be assumed that intensified production of spinal fluid due to loss of weight pressure may be a substantial factor in the genesis of the space form of motion sickness. The increased permeability of vascular barriers in weightlessness is conformed by the appearance of tissular flaccidity ["pastiness"]. The well-known fact that reactivity to drugs changes under the influence of flight factors is also indicative of increased permeability of the hematoencephalic barrier in weightlessness. L. S. Shtern attributed the change or distortion of the body's reaction to pharmacological agents to impairment of barrier function of the hematoencephalic barrier [15]. Redistribution of body fluids in a cranial direction, particularly of spinal fluid, may be instrumental in elevation of intracranial pressure in weightlessness. Thus, elevation of intracranial fluid pressure per se could be the immediate cause of nausea and vomiting in weightlessness. There is virtually no manifestation of the mechanism of elevation of intracranial pressure in the presence of signs of motion-sickness on the ground. Evidently, redistribution of pressure in lymph of the ear to the walls of the membranous labyrinth, when conditions are created for prolonged stimulation of sensory endings of the trigeminal nerve in its walls, is significant to development of motion sickness on the ground.

Thus, on the basis of the obtained data pertaining to the significance of sensory afferent innervation of the vestibular system, we believe that one of the mechanisms of onset of vestibulovegetative manifestations of motion sickness is related to the existence of an independent reflex pathway of vestibulovegetative reactions, with the sensory trigeminal nerve as the starting element and the reticular formation and hypothalamus as central elements (trigeminal reflex). From this point of view, the vestibular system as the triggering element of the seasickness reaction plays the role of trigger zone for vestibulovegetative reflexes implemented via the afferent trigeminal nerve of the fifth pair of cranial nerves. The trophics of the vestibular system, determined by the function of the hematolabyrinthine barrier and possible disturbances referable to intralabyrinthine pressure are significant to the mechanism of onset of the vestibulovegetative syndrome.

The expounded hypothesis enables us to explain the efficacy of a number of measures used to prevent vestibulovegetative motion sickness reactions. Rapid extinction of the vomiting reflex by chewing gum, sucking on caramels, inhaling ammonia fumes [16], chemical treatment of the nasal mucosa and nociceptive stimulation by biting on the lip or electric stimulation of the skin over the arm [17] could be attributed to the fact that there is central control of passage of sensory information to the brain in the system of the trigeminal nerve [18]. The nonspecific effect of acupuncture, which enhances vestibular stability [19], and attenuation of vestibulovegetative disorders by analgesia [20] evidently are related to their effects on the reticular formation and nociceptive centers. The mechanism of these effects can be explained, in this case, by the change and normalization of function of central structures of the nonspecific afferent nervous system--the reticular formation and hypothalamus.

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NEW BOOK ON PROGNOSIS OF BORDERLINE STATES REVIEWED

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[Review by Ye. A. Kovalenko of book "Prognozirovaniye sostoyaniy na grani normy i patologii" [Prognosis of Borderline States Between Normal and Pathology] by Prof R. M. Bayevskiy, Moscow, Meditsina, 1979, 298 pages]

[Text] Prognostication of various states and diseases of man is one of the most important directions of development of modern medicine. With increase in duration of space flights, prognostication acquired much importance in space medicine as well. At the same time, the needs of cosmonautics lead to development of other branches of science, in particular, development of new conceptions in applied physiology and preventive medicine. The book by Prof R. M. Bayevskiy, who is a well-known specialist in the field of space cardiology and physiological research during space flights, is a graphic example of this. The main ideas and methodology contained in this book are based on experimental data and experience in space medicine. It is expressly on the basis of problems of medical support of long-term manned space flights that the author developed methods of predicting states by evaluating the strain on regulatory systems and determining the direction of adaptive reactions.

The book starts with a chapter dealing with the bases of forecasting theory and application thereof to medicine and physiology. We can concur with the author that prognosis of states of healthy man when he is exposed to diverse factors is among the problems that are rather highly vague. For this reason, the classical probabilistic-statistical approach is applicable only for some very narrow problems. Changes in the condition of healthy man, particularly borderline ones, are characterized not only by significant vagueness of functional manifestations, but lack of clearcut classification. For this reason, special analysis is made of the object of the forecast, the health status.

There are several transitory states between normal and pathology, which have not yet been sufficiently studied. These states were named prenosological, and expressly they are the main object of forecasting. The gradation of such states can be considered in the form of qualitative microjumps preceding the macrojump, from normal to pathology. From these vantage points, analysis was made of the concept of health and disease, as well as conceptions of adaptation processes. It is remarkable that the author views energy mechanisms on the cellular level as the basic element of adaptation of the organism to environmental conditions.

Evaluation of the degree of strain on regulatory systems as the "price" of adaptation is one of the important aspects of the conception that the author expounds of forecasting states.

The section of the book, which describes methods for prognostic evaluation of states, is of great scientific and practical interest. The cardiovascular system is viewed as an indicator of adaptive reactions of the whole organism. The author successively discusses methods of evaluating the level of functioning of physiological systems, degree of strain on regulatory mechanisms and functional reserve. We must call attention to his use of mathematical analysis of cardiac rhythm to assess the strain on regulatory mechanisms. Changes in heart rate are a universal reaction of the body to any load. However, the mean pulse rate reflects the ultimate result of many regulatory influences on the circulatory system. Information about the function of controlling mechanisms is contained in the functions of "scatter" of a successive series of cardiac intervals. Use of methods of statistical, autocorrelation and spectral analysis makes it possible to retrieve discrete information about the state of various elements of the system that controls the heart rate and, consequently, to assess the strain on regulatory systems. No doubt, the reader's attention will also be attracted to other original methods for forecasting states, particularly those based on studies of circadian rhythms of physiological functions, the phase plane method and others.

The results of model investigations are submitted in the book to test the proposed principle for forecasting states and the described methods. In essence, there was modeling of factors used in space medicine practice, such as orthostatic and antiorthostatic tests, hypokinesia, time shift and seasickness. The results of these studies were not discussed from the standpoint of modeling adverse changes that are probable during space flights, but for examination of states that arise on the borderline between normal and pathology. The author demonstrated convincingly that, regardless of the type of factor, one observes the same successive stages of the adaptation process: first a strain on adaptive mechanisms, then stress and asthenization, with development of premorbid states on the borderline of impaired adaptation. The specifics of the factors do not affect the stages of adaptive reactions, merely determine the specifics of premorbid states and nosological forms occurring as a result of adaptation.

The sections of this book that deal with prediction of physical capacity of man and his mental efficiency will be of definite interest to specialists in space medicine and physiology. There, specific methodological procedures and examples of the results of forecasting states are given. Sources of information and the main principles of short-, medium- and long-term forecasting are discussed as they apply to prediction of physical capacities. Prediction of mental fitness is discussed as it relates to operator work and work loads with prevalence of a nervous and emotional component. Here, all prognostic ratings are derived on the basis of analysis of autonomic implementation of central nervous system activity with regard to receipt and processing of information. The author's own experimental material and extensive data from the literature illustrate the efficacy of such an approach. However, one should also mention one flaw: in this section there is no discussion of informational parameters characterizing the results of operator performance and mental work.

A sizable chapter of the book deals with mass scale prognostic examination of blue and white collar workers at industrial enterprises. A basically new approach is

described for settling problems of dispensary care for essentially healthy individuals. The essence of this approach is that determination is made of degree of adaptation of the body to the ambient industrial and socioecological environment in the course of the mass physicals, rather than premorbid states or diseases. This makes it possible to evaluate the health structure of different population groups and subsequently perform an in-depth medical examination only of individuals whose condition borders on impairment of adaptation. This chapter submits many data, obtained from examinations performed at several industrial enterprises. The results of these studies make it possible to offer long-term forecasts of the health of the population and manpower resources.

On the whole, the book by Prof R. M. Bayevskiy should be viewed as one of the first attempts at summing up experience in predicting borderline states, gained in space medicine, sports physiology, engineering psychology and preventive medicine. The conditions have been created for subsequent deeper theoretical investigation of this problem. The book will be of great interest to a wide circle of specialists, scientists and practicing physicians. It should be of particular interest to physiologists, physicians, biologists working in the field of space medicine, where the problem of evaluating borderline states occupies a focal place.

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NEW BOOK ON FUNCTIONAL BIOCHEMISTRY OF OSSEOUS TISSUE

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[Review by R. A. Tigranyan of book "Funktsional'naya biokhimiya kostnoy tkani" [Functional Biochemistry of Bone Tissue] by V. P. Torbenko and B. S. Kasavina, Moscow, Izdatel'stvo Meditsina, 1977, 272 pages]

[Text] The last few years have been characterized by increasing interest on the part of the most varied specialists in mineralized tissues, which could serve as the object for demonstrating the patterns of processes of biosynthesis of organic macromolecules, studies of crystalline structure of the mineral constitutent determining the mechanical properties of osseous and other tissues. Refinement of methodological approaches, the intensive development of biochemistry, general and molecular biology, medicine, biophysics and other sciences have created the conditions for in-depth studies of osseous tissue and the bone system as a whole. At present, it has become possible to study osseous tissue on the cellular, subcellular and molecular levels. Use of x-ray diffraction, electron microscopy, phase spectrography, radioactive isotopes, histochemical and other techniques revealed the ultrastructure of bone cells--osteoblasts and osteoclasts, which are directly involved in processes of biosynthesis and catabolism of components of the organic matrix of osseous tissue. Their role was demonstrated in regulating bone metabolism under normal and pathological conditions.

The book under review is of definite interest to specialists in the field of space biology and medicine. Such factors as weightlessness, hypokinesia and accelerations that every cosmonaut encounters in flight have an appreciable effect on the bone system. Long-term immobility could lead to an unbalanced mineral metabolism, loss of calcium by the skeleton and development of osteoporosis.

This monograph summarizes the extensive data in the literature and the authors' own material on biochemistry of osseous tissue. The monograph consists of eight sections, which deal with metabolic activity of bone cells, composition of the organic matrix of osseous tissue, composition and structure of mineral components. Mineralization of osseous tissue is significantly determined by the properties of the organic constituents of bone--collagen, noncollagen protein, mucopolysaccharides, lipids and others.

Osseous tissue is described in the book with conviction and in an interesting way as a living system that reacts rapidly to exogneous and endogenous changes. In

addition to enormous mechanical strength, high metabolic activity and variability of composition are inherent in human and animal bones.

The monograph discusses in detail processes of mineralization of osseous tissue, the role of hormones, vitamins and enzymes in metabolism thereof. There is demonstration of the finely balanced correlations between the skeleton, endocrine gland function and levels of vitamins in the body. A significant place is devoted in this book to age-related changes, as well as general and local metabolic disorders associated with various pathological states of the bone system. All of the data submitted create an idea about osseous tissue as a living and amazingly coordinated entity.

A special section deals with the effects of the environment on metabolism of osseous tissue. It discusses the effects of space flight factors (weightlessness, hypokinesia), ionizing radiation, the role of nutrition and others. Numerous studies of recent years yielded new data in the area of studying space flights, which made it possible to offer a new interpretation of the effects of various factors on the bone system. The results of these studies have already made a practical impact, which refers to development of a set of measures, including more exercise [physical load] for the skeletomuscular system, strictly controlled balanced diet and other measures directed toward maintaining mineral equilibrium of the organism.

We should mention the authors' critical approach to various aspects of the problem in question. The data in this book inspire new work in the field of biochemistry of bone tissue. This book is of interest to biochemists, orthopedist-traumatologists and scientists concerned with problems of life support under extreme conditions.

While we rate the book highly, we can make a few comments. First of all, we should mention the location of some chapters, which is not quite good. For example, the section on "Enzymes" should, in our opinion, have preceded the description of hormones and vitamins. Unfortunately, there is no special section in the book to deal with biochemical methods of studying osseous tissue, and this would not have been superfluous in our opinion. Finally, in the section dealing with the study of the effects of space flight factors, the data are not complete enough, and virtually none of the results of studies pursued in recent years aboard the Cosmos series of biosatellites is given. All this gives us grounds to raise the question of desirability of publishing a special book in the Soviet literature, which would deal with the effects of space flight factors on metabolism of osseous tissue.

The monograph under review could serve as a guide on various questions of biochemistry of bone tissue and, no doubt, it will be favorably received by broad circles of specialists in disciplines bordering on biochemistry. In the Soviet literature, no monographic works dealing with biochemistry of osseous tissue have been published. Publication of the book, "Functional Biochemistry of Bone Tissue," has filled this gap. The book may serve as the foundation for future generalizations in different branches of science, particularly space biology and medicine.

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NEW BOOK REVIEWED DEALING WITH EFFECTS OF HIGH AND LOW TEMPERATURES

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian Vol 15, No 3, May-Jun 81 p 94

[Review by R. F. Afanas'yeva of book "Fiziologo-gigiyenicheskiye aspekty deystviya vysokikh i nizkikh temperatur" [Physiological and Hygienic Aspects of the Effects of High and Low Temperatures], by A. N. Azhayev, Moscow, Izdatel'stvo "Nauka", 1979, 262 pages]

[Text] The book by A. N. Azhayev deals with studies of the effects of high and low temperatures on man, means of personal protection against adverse microclimate conditions.

This book summarizes the results of many of the author's studies, as well as data referable to about 700 works by Soviet and foreign researchers.

In Chapter 1, the author discusses current methods of studying man's thermal state. New methods for estimating mean temperature, a method of indirect determination of rectal temperature according to measurements of body temperature in other regions merit attention. There are some unfortunate mistakes (which do not lead specialists into error) with regard to designation of thermophysical units. The unit of measurement of thermal energy should be kJ/h rather than kJ (pp 16 and 17) and the unit of power should be W, and not W/h (p 27). Temperature difference in the formulas should be considered as a function of time (p 15).

Chapters 2 and 3 deal with the effects of high temperatures on man. Some rather important data are given about maximum accumulation of heat in the body. The latter was estimated by means of a new method of determining mean body temperature. The author conducted some interesting research on the combined effect of high temperature and certain other factors, heat transfer in man during exposure to long-wave infrared radiation from three sides. The author discussed the effects of high temperature on fluid-electrolyte metabolism, hemodynamics and O_2 tension in human blood as related to degree of overheating.

His study of the effects of high temperatures on the body enabled the author to undertake the choice of physiological criteria for evaluating man's thermal state.

In Chapter 4, there is comprehensive discussion of individual protection of crews of flying vehicles against high ambient temperatures. Data from the literature and the author's own studies enabled him to make the generalization that it is imperative to be governed by the principles of guaranteed and differentiated

thermal insulation, automatic heat regulation and complex solution of the problem of thermal protection as a whole in designing active protective gear.

Chapter 5 submits data on the effects of low temperature on man's thermal state. Questions of degree of generalized and local cooling of different parts of the body- and determination of the required thermal insulation to protect them merit attention.

In Chapter 6, the author systematizes the literature and his own data on personal protective gear against low temperatures. Table 48, which lists the wind chill factor, does not give complete information about which temperatures are referable to the moderate [temperate] zone and which to the zone of increasing danger.

Chapter 7 deals with classifications of thermal states of man. Development of a classification of thermal states on the basis of changes in parameters of functional systems of the body that are involved in heat regulation is the main contribution of the author to theory and practice of aviation and space medicine, as well as physiology of heat transfer in general. The criteria given in the book for evaluation of extent of overheating and cooling of man may also be used for purposes of ongoing medical monitoring.

It must be stated that there is no precedent in our or foreign literature for dealing in one book with experimental data on the effects of plus and minus temperatures, and if only for this reason publication of this book is very important.

The final section of the book is of definite interest; there, the author discusses the means of solving problems of regulating labor on the basis of examining the combined effect of factors of the industrial environment on the condition and efficiency of flight crews.

While we give this work a rather good rating, we cannot fail to mention that the author concentrated primarily on changes in human physiological functions under the influence of high and low temperatures at rest or while performing light work. Questions of evaluating thermal states when man performs heavy and moderate physical labor were left untouched. We should like to recommend that the author deepen his research in this important direction.

On the whole, in spite of the mistakes we mentioned in designating physical units, the book is quite interesting and will definitely be of great benefit to specialists in aviation and space medicine, physiologists, pathophysiologists and hygienists specializing in the area of research on the effects of microclimate, regulation of labor and development of personal protective gear.

ABSTRACTS OF ARTICLES FILED WITH THE ALL-UNION SCIENTIFIC RESEARCH INSTITUTE OF MEDICAL AND MEDICOTECHNICAL INFORMATION

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EFFECT OF TRAUMA ON ENDURANCE OF DECOMPRESSION

[Abstract of article by V. V. Vlasov, A. A. Voronov and P. M. Shalimov]

[Text] After prior exposure to high air pressure, rats were submitted to decompression equivalent to an altitude of 500 m. Animal endurance was evaluated by the incidence of deaths and average severity of disease.

Endurance of the rats of decompression diminished slightly when trauma was inflicted (fracture of leg) on the decompression "Plateau." As the time between trauma and decompression increased, animal resistance increased. The period of diminished resistance constituted 17 h after hypodermic injection of formaldehyde into the back, after which it increased. At the early stage following trauma and particularly after injection of formalin, there was concentration of blood subsequently followed by hemodilution. The changes in hematocrit and resistance, which occurred in stages, make it possible to compare decline and increase in resistance to phases of shock and countershock of the general adaptation syndrome. At the same time, preventive injection of corticosterone, hydrocortisone or cortisone to the rats did not lead to apprecialbe changes in resistance, in spite of overt clinical manifestations of the effect of cortisone in the case of long-term exposure.

Determination was made of individual maximum endurance of air pressure of 8 kg/cm^2 by cats, after which no disease occurred within 2 min of decompression. Seven days later, the hind leg was amputated with loss of 10% of blood. Experiments were repeated 1-3 days after this operation, increasing individual exposure by 2 min. Under such conditions, disease developed in intact animals and not in the operated ones. In these animals, there was less marked decrease in concentration of pyruvic acid, total cholesterol or increase in total lipids, β-lipoproteins and total protein of blood serum than in intact animals with caisson's disease. The cats' resistance reverted to the initial level 10-14 days after surgery.

Thus, while severe injuries lead to diminished resistance to decompression in the acute period, mild trauma did not lead to appreciable increase in probability of development of caisson's disease. Following the decline in resistance, there was development of a phase of increased resistance, which was more marked and lasted longer.

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OPTIMUM VESTIBULAR 'COORDINATION' OF MAN WITH A MOVING DEVICE

[Abstract of article by I. Yu. Sarkisov]

[Text] A mathematical model was constructed of the system of six semicircular canals of the labyrinth. This model was used to study the effect of man's location in a moving device on function of the semicircular canals. Evaluation was made of situations, in which the vestibular effects may be minimal. There is discussion of accelerated rotation of the moving system about a stationary axis, regular procession, man's natural movements in an evenly revolving system, etc. The best (worst) orientation of man's head was found for each type of system movement, which leads to minimal (maximal) vestibular reaction. This makes it possible to solve problems of "coordination" of an operator with a moving device, in order to provide for a high degree of efficiency. A system is offered for testing the theoretical conclusions.

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